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Recent Trends in Inspection of Sterile Dosage Forms

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Philip E. M. Crooker, B.S. (Chem.), J.D.
Vice President – Technical
Parexel® International

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Introduction

- Who am I and how did I get here?
- My LinkedIn® profile - https://www.linkedin.com/in/philip-crooker-j-d-a972576/
- My biography on the Parexel® regulatory portal - https://regulatory.parexel.com/ex-healthcare-agency-experts/philip-crooker

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1. This presentation reflects the views of the author and should not be construed to represent FDA's views or policies.

2. This presentation is intended to convey general information only and not to provide legal advice or opinions. An attorney should be contacted for advice on specific legal issues.

3. Nothing in this presentation is an offer for legal representation, and nothing in this presentation is intended to create an attorney-client relationship.

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What You Can Expect From This Presentation

- Understand the differences between Form FDA 483 observations and charges listed in Warning Letters.
- How the US FDA Office of Manufacturing Quality (OMQ) assesses cases.
- Examples of violations for sterile products from recent Warning Letters.
- Standard requests and special paragraphs in recent Warning Letters for sterile products
- Tools for making effective responses to Form FDA 483 and Warning Letters.
- *Extra topic of interest* - some analysis from recent Warning Letters regarding cross-contamination and FDA policy.
- Recent developments that could affect how industry can expect to interact with FDA for CGMP enforcement cases.

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Setting Up The First Two Topics – Form FDA 483 Observations & Warning Letters and OMQ Case Review

- The discussion of these areas is based largely on a blog post that will be published on the Parexel® regulatory portal.

- https://regulatory.parexel.com/regulatory-blog-2

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Differences Between Form FDA 483 Observations and Warning Letters

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Differences Between Form FDA 483 Observations and Warning Letter Violations (1)

- What information is provided on the Form FDA 483?
  - "Descriptions of observations made when in the investigator's **judgment** (emphasis added by FDA) conditions or practices are significantly objectionable and would render the product adulterated or injurious to health.
  - The determination of whether any condition is violative is an agency decision made after considering all circumstances, facts and evidence.
  - The conditions the investigator observed MAY (emphasis added by FDA) be determined by the FDA to be violations after review of all the facts.

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Differences Between Form FDA 483 Observations and Warning Letter Violations (2)

- The combination of the Form FDA 483 observations and the investigator's discussion with management may be considered prior notice to comply with the law.
- Where can I find this information?
  - See the FDA Investigations Operation Manual (IOM), Sections 5.2.3 and 5.2.7 and FDA Regulatory Procedures Manual Sec. 10-2.
  - https://www.fda.gov/media/76769/download
  - https://www.fda.gov/media/71765/download

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Differences Between Form FDA 483 Observations and Warning Letter Violations (3)

- What is a Warning Letter (WL)?
  - Used by FDA to establish prior notice of violations; and
  - Give manufacturers an opportunity to take voluntary and timely corrective actions before FDA initiates enforcement action.
- Why is prior notice important?
  - The U.S. Food and Drug Cosmetic Act (FDCA) is a strict liability law.
  - The FDA has no obligation to warn firms that they are acting in violation of the law.
  - FDA policy – give firms an opportunity to voluntarily take corrective action before any enforcement actions are started.

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Differences Between Form FDA 483 Observations and Warning Letter Violations (4)

- To a large degree, this policy depends on ***trust*** – FDA presumes that the majority of firms will voluntarily comply with the law when it is given adequate notice.
- How does FDA determine when a firm has been given adequate notice? Several factors:
  - FDA has jurisdiction – the conditions or practices or product violates the FDCA.
  - The notice – in writing or verbally – identified what violated the law.
  - The notice was given to the most responsible persons for the manufacturer.
  - The manufacturer was given a reasonable time to implement corrective actions.
  - Consider if there were any conditions that affected delivering prior notice – such as change in ownership or management.

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Differences Between Form FDA 483 Observations and Warning Letter Violations (5)

- WL are intended to be sent only when the violations have regulatory significance.
  - These are situations where FDA could take enforcement action if the violations are not promptly corrected.
- The WL was created by FDA to correct violations of the statute or regulations.
  - More effective tool than relying on formal adjudication of individual cases.
  - Transparency and access – more reliable than using adjudication to announce policy.
- Using a WL does not prevent FDA from taking other actions at the same time or following a WL - such as administrative detention, seizures, and injunctions.

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Differences Between Form FDA 483 Observations and Warning Letter Violations (6)

- For CGMP cases, FDA may also take other actions as an alternative to or in combination with a WL – such as "import alerts" (or detention without physical examination (DWPE)).
- Using a WL is not appropriate when the following conditions exist:
  - History of repeat or continued similar (not necessarily the same) violations when the manufacturer has been given prior notice of those violations.
  - Intentional or flagrant violations.
  - When the violation presents a reasonable possibility of injury or death (*not the same as clinical significance*).
  - Intentionally false statements – written and orally – that cannot be retracted (see Title 18 U.S. Code §1001).
  - When notice has been given by other means and the violations have not been corrected.

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Differences Between Form FDA 483 Observations and Warning Letter Violations (7)

- Where can I find this information?
  - See the FDA Regulatory Procedures Manual (RPM) Sec. 4-1-2; 4-1-3; 4-1-15; and 10-2.

    - https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual
    - https://www.fda.gov/media/71765/download

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Differences Between Form FDA 483 Observations and Warning Letter Violations (8) – Summary

Form FDA 483	Warning Letter
Observations by investigators.	Violations of statute or regulations.
Significantly objectionable conditions.	Must have regulatory significance.
May be considered prior notice.	Presumed to provide prior notice.
Observations aligned with language in regulations.	Contains a statutory charge and example violations with specific references to 21 CFR § 211.
Copy given to most responsible person at manufacturer following close of inspection.	FDA not required to send WL prior to taking enforcement action(s).
Reviewed by CDER to determine whether observations constitute violations.	Written and reviewed by OMQ and may be reviewed by Office of Chief Counsel under certain circumstances.

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Office of Manufacturing Quality (OMQ) Case Review

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Simplified Case Process Flow

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Timelines

- After the inspection has been concluded, all the steps in the case process flow are governed by timelines.
- There are internal timelines that ORA and OMQ use to ensure that the case review meets all milestones to comply with the law.
- The public timelines are provided by the Generic Drug User Fee Act legislation (GDUFA) and commitment letter and also the “Concept of Operations” between ORA and OMQ.
  - https://www.fda.gov/drugs/pharmaceutical-quality-resources/questions-and-answers-integration-fda-facility-evaluation-and-inspection-program-human-drugs-concept

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OMQ Case Review Process (1)

- OMQ uses a standardized process with a patient health focus to review cases governed by various standard operating procedures (SOP).
- Determines different levels of violations.
- Manufacturing facilities are classified into different levels of quality assurance maturity based on the violation assessments.
- Uses semi-quantitative risk assessment of violations including site intrinsic risk and violation risk.
    - Builds on existing FDA risk evaluation of manufacturing – see https://www.ipqpubs.com/wp-content/uploads/2015/01/Tran_and-Morgan_micronization1.pdf
- Aggravating and mitigating factors are considered.
- Tailored enforcement actions to achieve voluntary compliance.

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OMQ Case Review Process (2)

- The administrative record for each case will typically include:
  - Information about the site.
  - The inspection findings (recommendations from ORA and the evidence collected during the inspection – typically the EIR and attachments).
  - Decision-making questions and guidance .
  - Case specific factors.
  - Firm's compliance history.
  - Aggravating and mitigating factors.
  - Recommendations for any enforcement action(s).

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OMQ Case Review Process (3)

- If OMQ determines that the case will result in a WL being sent to the manufacturer or other related parties (such as applicant holder), the WL should always contain these four parts:

1. What is the issue – use facts from the observations and why there is a violation of the law.
2. How the firm responded to the observations.
3. If the firm's response was inadequate explain why.
4. What FDA wants the firm to do in response to the WL.

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Examples of Recent Trends in Violations for Sterile Products

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August, 2019: WL 320-19-32 (Emcure Pharmaceuticals)

1. Violations & Facts

- Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).
  - ❖ You failed to adequately investigate the following sterility failures obtained during routine batch release testing…

2. Firm's response

- According to your sterility failure investigations, the most probable root cause for both events was laboratory error. Your firm's investigations substantially addressed the potential for microbial contamination during sterility testing, but deemphasized potential manufacturing causes.

3. Why firm's response was inadequate

- Your sterility failure investigations lacked sufficient data to support its conclusions. For example…

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June, 2019: WL CMS #578577 (AllerQuest LLC)

1. Violations & Facts

- Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups **(21 CFR 211.42(c)).**
  - ❖ You manufacture sterile injectable drug products in a facility that is not adequately designed or controlled for sterile drug operations.
- Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas (**21 CFR 211.42(c)(10)).**
  - ❖ Your firm had various departures from your established actions limits throughout your ISO 5 critical area and clean rooms but failed to adequately address them.
- Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed **(21 CFR 211.192).**
  - ❖ You found recurrent contamination of your sterile injectable drug products with foreign particulate matter, but you failed to adequately investigate and identify the root causes of the recurrent contamination.

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June, 2019: WL CMS #578577 (AllerQuest LLC) (2)

2. Firm's responses.

- In your response you committed to engaging third-party consultants to assist with the remediation of your facility. You also mention that all batches of your drug product have passed sterility testing for release.
- In your response, you committed to enhancing your EM program, remediating your HVAC system, and using automated systems to continuously monitor environmental conditions. You also discussed historical EM sampling results and sterility testing.
- In your response, you committed to revising your visual inspection SOP, establishing action and alert limits, and performing a risk assessment of drug products on the market.

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June, 2019: WL CMS #578577 (AllerQuest LLC) (3)

3. Why the firm's responses were inadequate.

- You failed to provide adequate supportive documentation to evaluate the effectiveness of your corrective actions and preventive actions (CAPA). Finished product testing alone is limited in its ability to establish sterility of all units because contamination is not normally uniformly distributed.
- You failed to provide adequate supportive documentation to evaluate the adequacy of your CAPA.
- You failed to determine the root cause of the particulate contamination. Product quality cannot be inspected into your drug product: it must be assured by an adequate production process. You also failed to provide adequate supportive documentation to evaluate the adequacy of your CAPA.

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June, 2019: WL CMS #568173 (Akorn Inc.)

1. Violations & Facts

- Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed **(21 CFR 211.192).**
  - ❖ Your investigations into out-of-specification (OOS) laboratory results and manufacturing deviations are inadequate and incomplete, do not include scientifically-supported conclusions, and lack prompt corrective action and preventive actions (CAPA). We reviewed numerous investigations that were open for more than six months; some were open for more than a year.
- Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes **(21 CFR 211.113(b)).**
  - ❖ Operators repeatedly displayed multiple poor aseptic practices during set-up and filling operations.
- Your firm failed to prepare batch production and control records with complete information relating to the production and control of each batch of drug product produced **(21 CFR 211.188).**
  - ❖ You failed to document in your batch record the lidocaine hydrochloride 2% jelly, USP Sterile, lot 8G37A leak during aseptic filling operations on July 7, 2018. Further, your investigation into a low OOS yield for this batch did not discuss the leak observed during filling.

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June, 2019: WL CMS #568173 (Akorn Inc.) (2)

2. Firm's Responses

- You opened a manufacturing investigation and first concluded that defects in bottles received from the supplier led to the OOS osmolality result.
- You first determined the root cause to be a laboratory procedure deficiency in March 2017. Later investigations noted the failures could be drug product-related. Your July 2017 Technical Assessment identified an error in the impurity calculation.
- Your investigation determined the OOS impurity result would have occurred at 14 months.

3. Why The Firm's Responses Were Inadequate

- This investigation was inadequate. You concluded the event was an isolated incident with no complaints received for the product. However, we identified several complaints you received for empty or leaking drug products for lots packaged in the implicated bottles.
- Your investigations remained open, you continued to recalculate test results to accurately report stability test data, and you had not yet determined a root cause for the OOS results
- Your response is inadequate. The details provided in your response did not clearly define management responsibilities relating to timeliness and the number of extensions that may be granted to an ongoing investigation. We acknowledge that you have initiated efforts to remediate your investigation programs; however, your response did not provide enough detail of your remediation or adequately specify how you will improve root cause determinations.

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March, 2019: WL 320-19-14 (Hospira Healthcare India Pvt. Ltd.)

1. Violations & Facts

- Your firm failed to ensure that laboratory records included complete data derived from all tests necessary to assure compliance with established specifications and standards **(21 CFR 211.194(a)).**
  - ❖ Your microbiology laboratory did not accurately report test results.

- Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed **(21 CFR 211.192).**
  - ❖ Your firm failed to adequately investigate poor control and critical defects in your [redacted] manufacturing process.

- Your firm failed to have, for each batch of drug product, appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release **(21 CFR 211.165(a)).**
  - ❖ From February 16 to March 20, 2018, you tested [redacted] batches of [redacted] API for [redacted]. All results were reported as passing. However, during the FDA inspection on March 28, 2018, we requested retesting the same batches under our observation. All retest results were OOS.

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March, 2019: WL 320-19-14 (Hospira Healthcare India Pvt. Ltd.) (2)

2. Firm's response

- Your written response acknowledged the significance of these microbial growth count discrepancies.
- In your response, you committed to enhance process understanding and control. You stated that you would improve and validate a modified process and remediate deficiencies in the visual inspection program.
- In your response, you indicated that your investigation had revealed data integrity issues related to reporting test results. You also indicated that your investigation, still in progress, has identified laboratory equipment failure as a probable root cause for the failing results. More specifically, inefficient removal of [redacted] from the [redacted] is considered to be the cause of incomplete [redacted] of the sample.

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March, 2019: WL 320-19-14 (Hospira Healthcare India Pvt. Ltd.) (3)

3. Why firm's response was inadequate

- Your response included adding corporate and third-party oversight of microbiology laboratory tests and data reporting, and several other remediation measures. However, your response did not describe the scope of inaccurate reporting of data, and the extent of management and staff involvement with data manipulation.
- Your response was inadequate in that: (1) It did not include a reassessment of the adequacy of your CAPA to address handling out-of-specification (OOS) results obtained by your laboratory; and (2) It lacked sufficient details on the evaluation of additional products produced with the same manufacturing equipment used for the injection.
- We acknowledge your decision to suspend all testing. However, you did not include an assessment to determine whether other QC laboratory tests performed in the same laboratory were compromised by data integrity issues. Your response also fails to discuss the extent of data integrity breaches in your facility

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February, 2019: WL CMS #558914 (Akorn, Inc.)

1. Violations & Facts

- Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes **(21 CFR 211.113(b)).**
  - ❖ Operators displayed poor aseptic practices during aseptic set-up and filling operations.
  - ❖ Our investigators observed non-integral packages containing sterile gloves and holes in the secondary packaging layer of your sterile wipes.
  - ❖ Your smoke studies performed for your ISO 5 areas also lacked simulation of multiple critical interventions that occur during aseptic manufacturing operations.

- Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups in aseptic processing areas **(21 CFR 211.42(c)(10)).**
  - ❖ Your environmental monitoring program is deficient.

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February, 2019: WL CMS #558914 (Akorn Inc.) (2)

2. Firm's Responses

- Engaged a third party to assist in efforts to re-train personnel and provide additional oversight of aseptic practices, and that you are revising procedures. Installing restricted air barrier systems (RABS), as previously committed in 2016. Plan to perform supplemental smoke studies for interventions not captured in the current studies and additional smoke studies once you install the new RABS.
- Commit to evaluate environmental monitoring program.
- Have performed targeted training on sanitization procedures. Further, you note that your disinfectant efficacy program demonstrates the ability of your agents to reduce bioburden.
- In your response, you state no other stability testing issues were noted with FDA-approved test methods.

3. Why The Firm's Responses Are Inadequate

- You did not provide a sufficient evaluation of all batches produced under inadequate conditions. You also did not commit to extensive redesign of your aseptic process operation.
- Your target completion date is December 31, 2019. You commit to tighten the glove limit for personnel monitoring, but only after "critical" interventions in the ISO 5 areas. Any personnel who perform activities within the ISO 5 area should meet your tightened glove limit.
- You have not determined the scope of these poor practices observed at your facility, including identifying employees involved and how long this has been occurring. You did not extend your investigation to determine if complete disinfection activities and proper documentation practices were followed.

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October, 2018: WL 320-19-01 (Hanlim Pharm. Co. Ltd.)

1. Violations & Facts

- Your firm failed to follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes **(21 CFR 211.113(b)).**
  - ❖ Your operators' poor aseptic practices during set-up and filling operations for your sterile eye drop solution posed a significant risk of microbial contamination.
- Your firm failed to establish an adequate system for monitoring environmental conditions in aseptic processing areas **(21 CFR 211.42(c)(10)(iv)).**
  - ❖ Your firm did not perform routine monitoring of viable organisms in the filling area inside the rigid barrier on Line 1.
- Your firm failed to exercise appropriate controls over computer or related systems to assure that only authorized personnel institute changes in master production and control records, or other records **(21 CFR 211.68(b)).**
  - ❖ Three of your quality control team leaders had administrator privileges within your HPLC computerized laboratory software system. Because they review and approve CGMP data, their access level should preclude file deletion or modification. In addition, two of your laboratory software systems had unlocked time and date functions, which allowed users to change the recorded dates and times of analyses.

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October, 2018: WL 320-19-01 (Hanlim Pharm. Co. Ltd.) (2)

2. Firm's Responses.

- Stated will make changes to the filling line and will train operators on movement in filling rooms.
- Stated would add two settling plates inside the Line 1 rigid barrier and train your operators. Also stated will conduct personnel monitoring of the operators who perform aseptic processing equipment setup.
- Stated would grant administrator privileges to only an information technology employee not involved in laboratory testing. Also stated that the time and date setting function for the system will be locked.

3. Why Firm's Responses Are Inadequate

- Your response was inadequate because you did not sufficiently assess the adequacy of your aseptic filling line design. You did not provide a detailed plan for qualifying changes to your filling line by conducting media fills and smoke studies. You also did not provide any details on operator training
- Although you stated in your response that you added monitoring locations, you failed to include the revised procedure for this change. You also did not fully evaluate the sufficiency of your overall environmental monitoring program (including personnel monitoring) to promptly identify potential routes of contamination and enable corrections before product contamination occurs.
- Your response is inadequate because you did not evaluate whether CGMP data were improperly modified or deleted, and you did not include supporting documentation for your proposed CAPA plan.

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September, 2018: WL 320-18-73 (Lernapharm Inc.)

1. Violations & Facts

- Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include validation of all aseptic and sterilization processes **(21 CFR 211.113(b)).**
  - ❖ You failed to adequately validate your drug manufacturing process for your drug products that you claim achieves "[redacted] sterilization."
- Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed **(21 CFR 211.192).**
  - ❖ You failed to conduct thorough investigations into customer complaints for your drug products which purport to be sterile. You did not evaluate all potential causes for customer complaints or extend the investigation to other potentially affected batches and other products.
- Your firm failed to use appropriate air filtration systems for production areas **(21 CFR 211.46(c)).**
  - ❖ Your firm manufactures [redacted] products, which purport to be sterile, in areas of insufficient control and air classification.
- Your firm failed to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups **(21 CFR 211.42(c)).**
  - ❖ You failed to establish a program to evaluate the microbiological quality of the environment in which you manufacture [redacted], which purports to be sterile.

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September, 2018: WL 320-18-73 (Lernapharm Inc.) (2)

2. Firm's Responses

- Your response states that you do not perform finished product sterility testing because you maintain written records and validation procedures for your parametric release "sterilization program."
- Your response acknowledges deficiencies in your investigation systems.

3. Why The Firm's Responses Are Inadequate

- Your response is inadequate. Your firm lacks an adequate sterilization method. You have not demonstrated an ongoing state of control and your products, which purport to be sterile, are produced using manufacturing methods that are inappropriate to support this claim.
- In addition, parametric release is only appropriate for robust sterilization methods (e.g., steam sterilization). The robust sterilization method must also be augmented by a strong sterility assurance program, an extensive ongoing characterization of batch process control, and a vigilant quality system.
- Your risk assessment addressing loss of product sterility due to packaging "deterioration" was inadequate. Further, you determined that 18 other batches could have been affected by debris on the sealing [redacted], but you provided no information regarding your investigations into the additional batches.

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Locations for WL Examples

- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/emcure-pharmaceuticals-limited-576961-08022019.
- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/allerquest-llc-578557-06242019
- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/akorn-inc-568173-06132019
- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/hospira-healthcare-india-pvt-ltd-557890-03042019
- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/akorn-inc-558914-02042019
- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/hanlim-pharm-co-ltd-553021-10032018
- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/lernapharm-loris-inc-552525-09042018

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What Does FDA Want – Examples of Standard Requests & Special Paragraphs

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Standard Requests and Special Paragraphs

- FDA has increased its use of standard requests in WL to improve the quality of notice so firms can remediate more effectively. Topics can include:

  - OOS issues.
  - Stability.
  - Laboratory systems
  - Component and finished product release testing.
  - Water systems.
  - Aseptic process and technique.
  - Cleaning validation.
  - Process validation.
  - Contractor oversight.
  - Data integrity.

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Standard Requests and Special Paragraphs (2)

- FDA also uses a variety of special paragraphs in WL for policy – these are not charges or violations.
- FDA periodically creates new language as needed based on case analysis and trends. Frequent topics cited in WL include:

  - OOS issues.
  - Corporate oversight when there are repeat violations at the same or multiple facilities.
  - Quality systems.
  - CGMP consultant recommended.
  - Various FDCA 501(j) violations – delay, deny, limit or refuse an inspection.
  - Aseptic processing.
  - Data integrity.
  - ICH Q7A guidance.

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August, 2019: WL 320-19-32 (Emcure Pharmaceuticals)

4. What Does FDA Want – Standard Requests For **Investigations**

- An assessment of your overall system for investigations of deviations, atypical events, complaints, out-of-specification results, and failures. Your corrective action and preventive action (CAPA) plan should include, but not be limited to, improved rigor in reviewing the sources of variation in your operation that may cause deviations, failures, or defects. Also include your process for evaluating CAPA effectiveness.
- A comprehensive, third-party evaluation of records relating to discrepancies, deviations, complaints, maintenance, detailed batch defect history, and investigations related to potential sealing variability and container-closure integrity issues. Include all lots since July 2016 in the review. Based on this evaluation, provide an updated retrospective review to assess the robustness of your sealing process and container-closure systems.
- Your plans and procedures to ensure that future sterility failure investigations include a comprehensive evaluation of potential vulnerabilities in the manufacturing operation, specifically but not limited to a review of uniformity of biological lethality in your sterilizer as well as container-closure system integrity.
- Due to your finding of turbid samples during multiple additional sterility tests since 2017 beyond those discussed in this letter, provide a comprehensive third-party review of your sterility test methods. Special emphasis should be placed on improving method robustness to eliminate the root causes of the variations that led to the apparent false turbid readings.
- A third-party review of your sterilizer reliability, with emphasis on uniformity of heat distribution and lethality throughout your sterilizers. This review should fully assess both physical and biological data and include analysis of current F-value and Z-value data, and any related assumptions incorporated into your sterilization cycle justifications. Include detailed analysis of temperature mapping/load studies, D-value determinations for each biological indicator lot, and causes of any positive biological indicator results. Specify the [redacted] (or positions that had widest variation) identified in each of your validation studies since 2017.

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August, 2019: WL 320-19-32 (Emcure Pharmaceuticals) (2)

4. What Does FDA Want – Special Paragraph for **Repeat Observations**

- In a previous inspection, dated August 7 to 17, 2017, FDA cited similar CGMP observations in which you inadequately performed microbiological investigations. Repeated failures demonstrate that executive management oversight and control over the manufacture of drugs is inadequate.
- Your executive management remains responsible for fully resolving all deficiencies, and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured conform with CGMP requirements.

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June, 2019: WL CMS #578557 (AllerQuest LLC)

4. What Does FDA Want – Standard Requests For **Aseptic Practices**

- Your interim plans for the manufacture and distribution of your sterile drug products while you remediate your facility and equipment design, and all other inadequacies.
- Comprehensive identification of all contamination hazards with respect to your aseptic processes, equipment, and facilities. Provide 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 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.
- Detailed supportive documentation of your CAPA.
  - ❖ Include detailed updates on your plans for facility remediation including how you will assure adequate separation of the ISO 5 critical area from unclassified areas. This plan should include how you will address all filling operations (ampule and vial filling).
  - ❖ Include your change-over procedures for your ampule filling and vial filling operations as well as updated smoke studies of ampule filling and vial filling operations after remediation of your facility.
  - ❖ Provide a detailed description of equipment changeover practices between the ampule filling machine and vial filling machine in the ISO 5 curtained area. Include details such as how equipment is moved around the facility, disassembled, stored, and installed for production.

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June, 2019: WL CMS #578557 (AllerQuest LLC) (2)

4. What Does FDA Want – Standard Requests For **Environmental Monitoring**

- Detailed supportive documentation of your CAPA, including but not limited to:
  - ❖ Historical environmental monitoring data you referenced in your response as well as historical environmental monitoring data from all of your cleanrooms, with designation whether the result was obtained within the ISO 5, ISO 6, and ISO 7 zone (also include exact location of the sample). Also, provide a detailed summary of all environmental monitoring data that exceeded alert and action limits for the past two years.
  - ❖ A detailed plan to ensure routine monitoring and recording of temperature, pressure, and humidity. Include your provisions to ensure deviations from established limits will generate alarms and be fully documented and adequately investigated.
- Your detailed procedure for routine shutdown and startup of aseptic production operations to significantly improve assurance that the environment is in a robust state of control before production may recommence.
- Comprehensive independent review of your disinfection program and a CAPA plan. The latter should include but not be limited to enhanced use (e.g., increased frequency) of sporicidal agents in your disinfectant program.

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IPA Innovation, Quality and Global Reach

June, 2019: WL CMS #578557 (AllerQuest LLC) (3)

4. What Does FDA Want – Standard Requests For **Investigations**

- Detailed supportive documentation of your CAPA including, but not limited to, your risk assessment.
  - ❖ Your assessment should include an adequate root cause analysis for the recurring particulates, thorough identification of the particulates, and their corresponding origin (intrinsic or extrinsic).
  - ❖ You should also address any drug product quality or patient safety risks and assess the adequacy of investigations into any deviations, out-of-specification results, or other manufacturing quality issues. Include a full CAPA (e.g., notification to customers, recall, etc.) for any drug products that may have quality or safety risks.
  - ❖ An improved visual inspection program. Your program should include acceptance and rejection limits for each batch of drug product. The limits should be based on sound statistical principles for the evaluation of particulates in sterile injectable drugs.
- A comprehensive, independent assessment of your system for investigating deviations, atypical events, complaints, OOS results, and failures. Your CAPA plan should include, but not be limited to, improvements in investigations, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA plan effectiveness.

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IPA Innovation, Quality and Global Reach

June, 2019: WL CMS #578557 (AllerQuest LLC) (4)

4. What Does FDA Want – Special Paragraph for **CGMP Consultant**

- Your consultant should be qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

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June, 2019: WL CMS #568173 (Akorn Inc.)

4. What Does FDA Want – Standard Requests for **Investigations**

- A comprehensive, independent assessment of your system for investigating deviations, atypical events, complaints, OOS results, and failures. Your CAPA plan should include, but not be limited to, improvements in investigations, root cause analysis, written procedures, and quality unit oversight. Also include your process for evaluating CAPA plan effectiveness. Provide an evaluation of all open investigations for batches that remain on the market and include the length of time investigations are open.
- A retrospective, independent review of all invalidated OOS (in-process and finished testing) results obtained for products currently on the U.S. market. Assess whether the scientific justification and evidence for each invalidated OOS result was conclusive. For investigations that conclusively establish laboratory root cause, determine effectiveness of the CAPA, and ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS results with inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of the manufacturing steps, raw materials, process capability, deviation history, batch failure history). Provide a CAPA plan that identifies manufacturing root causes and specifies meaningful improvements.
- Review and remediate your overall system for investigating OOS results. Provide a CAPA plan to improve OOS handling. Your CAPA plan should ensure that your revised OOS investigations procedure includes enhanced quality unit oversight of laboratory investigations, identification of adverse laboratory control trends, resolution of causes of laboratory variation, and investigations of potential manufacturing causes when a laboratory cause cannot be conclusively identified.

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June, 2019: WL CMS #568173 (Akorn Inc.) (2)

4. What Does FDA Want – Standard Requests for **Stability**

- A comprehensive, independent assessment and CAPA plan to ensure the adequacy of your stability program. Your CAPA plan should include, but not be limited to:

  - ❖ A remediated SOP describing your stability program
  - ❖ Stability indicating methods.
  - ❖ Stability studies for each drug product in its container-closure system before distribution is permitted.
  - ❖ An ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid.
  - ❖ Specific attributes to be tested at each station.
  - ❖ An evaluation of the timeliness of your stability study testing

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June, 2019: WL CMS #568173 (Akorn Inc.) (3)

4. What Does FDA Want – Standard Requests for **Laboratory Systems**

- An update to your investigation into data associated with your legacy equipment and data deletion.
  - ❖ An update on your investigation into the [redacted] database deletion.
  - ❖ An update on your investigations into the unreviewed HPLC injection sequences. Identify the root causes for these lapses and the CAPAs you have implemented, or plan to implement, to prevent recurrence. Include an update on CAPA effectiveness that will help ensure the adequacy of the CAPAs listed in your September 21, 2018, response and any additional CAPAs identified during your investigations.
- A comprehensive, independent review of your laboratory practices, procedures, methods, equipment, and analyst competencies. Based on this review, provide a detailed CAPA plan to fully remediate your laboratory system. Your plan should include the process you will use to evaluate the effectiveness of the implemented CAPA plan.
- We note that some initial efforts toward laboratory system remediation have been undertaken, including laboratory equipment upgrades. As part of your detailed CAPA, include an update on your new laboratory operations, including a timeline for qualification and transfer of testing onto new instruments. Also include a list of all new equipment and existing equipment that will be used in the new laboratory.

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June, 2019: WL CMS #568173 (Akorn Inc.) (4)

4. What Does FDA Want – Standard Requests for **Aseptic Practices**

- A comprehensive, independent identification of all contamination hazards with respect to your aseptic processes, equipment, and facilities. Provide an independent risk assessment that includes, but is not limited to:
  - All human interactions with the ISO 5 area
  - Equipment placement and ergonomics
  - Facility layout
  - Personnel flow
  - Material flow
  - Room space
- A detailed CAPA plan, with timelines, to address the findings of the contamination hazards risk assessment. The plan should address how you will improve aseptic processing facility and equipment design, process control, personnel practices, and other deficient elements of your current operation.
- Improvements in operations management that will ensure aseptic practices and cleanroom behavior during production. Include steps to better assure routine and effective supervisory oversight for all production batches. Also describe the frequency of quality assurance oversight (e.g., audit) during aseptic processing and other operations. As part of your assessment, summarize your review of past processing videos, including all batches with leak problems manufactured within three years of the date of this letter. Provide the batch number, date of processing, extent of leak, and assessment of batch quality.
- Your full investigation into the leakage during filling of lidocaine hydrochloride 2% jelly, USP Sterile, lot 8G37A. Provide an assessment of filling line hoses, connector assemblies, cleaning, maintenance, and operator set-up procedures.
- A thorough risk assessment that evaluates how poor aseptic technique and cleanroom behavior, such as those observed during the inspection, may have affected quality and sterility of your drugs.
- An update on the third-party assessment of your media fill program. Include your plan for implementing the recommendations in the assessment.
- A description of improvements made in your latest media fills to more accurately and appropriately simulate interventions that occur during production.

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June, 2019: WL CMS #568173 (Akorn Inc.) (5)

4. What Does FDA Want – Special Paragraphs

- **Additional Guidance on Aseptic Processing:** See FDA's guidance document Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070342.pdf.
- **Quality Systems Guidance:** Your firm's quality systems are inadequate. For guidance on establishing and maintaining CGMP compliant quality systems, see FDA's documents:
  - Q8(R2) Pharmaceutical Development, at https://www.fda.gov/media/71535/download
  - Q9 Quality Risk Management, at https://www.fda.gov/media/71543/download
  - Q10 Pharmaceutical Quality System, at https://www.fda.gov/media/71553/download
- **Repeat Violations at Multiple Sites:**
  - FDA cited similar CGMP violations at other facilities in your company's network. On January 4, 2019, Akorn, Inc. (FEI 1450114) was issued a Warning Letter, for among other violations, inadequate controls for manufacturing sterile drugs.
  - These repeated failures at multiple sites demonstrate that management oversight and control over the manufacture of drugs are inadequate. Your executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems, processes, and the products you manufacture conform to FDA requirements.

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June, 2019: WL CMS #568173 (Akorn Inc.) (5)

4. What Does FDA Want – Special Paragraphs

- **Data Integrity Remediation – Expanded**
  - Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download.
  - We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.
  - In response to this letter, provide the following…
- ***Quality Assurance Program Audits***
  - FDA reminds Akorn of their responsibility as a matter of CGMP to correct deficiencies found during quality assurance program audits, also referred to as "internal audits" in your correspondence with the FDA.
  - In response to this letter, conduct a review of all quality assurance program audits and inspections within the last five years at all Akorn facilities. Provide written certification that required corrective actions for such audits and inspections have been taken. If, upon your review or the review by any pertinent party working on your behalf, it is determined that actions have not been taken, provide a timeline for completion for all related corrective actions identified in the audits. The certification and/or timeline should be signed by the CEO of Akorn.

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March, 2019: WL 320-19-14 (Hospira Healthcare India Pvt. Ltd.)

4. What Does FDA Want – Standard Requests for **Process Controls**

- Your final report on the improvements needed to ensure that [redacted] processes will reproducibly meet required quality attributes.
- An evaluation of the design and state of control of each [redacted] cycle used to produce drug products for U.S. supply. Include a retrospective assessment of all investigations (e.g., process deviations, failures, complaints) related to [redacted]drug products not recalled from the U.S. market. Summarize the root causes assigned for identified defects, the adequacy of the CAPA, and any further steps needed.
- Your CAPA for routine, vigilant operations management oversight of facilities and equipment to assure prompt detection of equipment performance issues, execution of repairs, completion of preventive maintenance, upgrades to equipment and facilities, and other appropriate actions.

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March, 2019: WL 320-19-14 (Hospira Healthcare India Pvt. Ltd.) (2)

4. What Does FDA Want – Special Paragraphs

- **Data Integrity Remediation - Expanded**
  - Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download.
  - We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.
  - In response to this letter, provide the following…
- **Cessation of Manufacturing at the Facility**
  - We acknowledge your decision to cease all production and distribution of drug products from the site due to the significant long-term loss of product demand. We also acknowledge your commitment for third-party consultants to continue performing product quality assessments, including ongoing review of adverse events and customer complaints for drugs remaining in distribution from this facility.
  - Note that remediating these CGMP violations will be necessary if Pfizer, a successor, or an acquirer resumes drug manufacturing operations at this site for the U.S. market.

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February, 2019: WL CMS #558914 (Akorn, Inc.)

4. What Does FDA Want – Standard Requests for **Aseptic Processes**

- 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.
- Your plan to ensure appropriate aseptic practices and cleanroom behavior during production. Include specific steps to ensure routine and effective supervisory oversight for all production batches. Describe the frequency of quality assurance oversight (e.g., audit) during aseptic processing and other operations. Also, provide your protocol and an update on your third party's independent assessment of your aseptic practices. As part of your assessment, summarize your review of past processing videos.
- A thorough risk assessment that evaluates how poor aseptic technique and cleanroom behavior, such as those observed during the inspection, may have affected quality and sterility of your drugs.
- A description of the extent of the missing batch record entries for interventions performed. Detail how you will remediate your system for recording interventions while also not adding further contamination risks to your products.
- A review of your supplier qualification, monitoring, and maintenance program to ensure you adequately address the quality of the materials brought into the cleanroom. Include a review of all materials, including but not limited to, disposable materials (e.g., sterile gloves and wipes) to ensure integrity and prevent contamination in the aseptic processing operation.
- A copy (e.g., a video file) of your new smoke study recordings and a detailed description or schematic of the RABS extension used to provide local protection of the stopper hopper area. Provide an independent assessment of the smoke studies.

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IPA Innovation, Quality and Global Reach

February, 2019: WL CMS #558914 (Akorn, Inc.) (2)

4. What Does FDA Want – Special Paragraphs

- **Additional Guidance on Aseptic Processing:** See FDA's guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, at https://www.fda.gov/downloads/Drugs/Guidances/ucm070342.pdf.
- **Quality Systems:** Your firm's quality systems are inadequate. For guidance on establishing and following CGMP compliant quality systems, see FDA's guidance for industry:
  - *Q8(R2) Pharmaceutical Development*, at https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf;
  - *Q9 Quality Risk Management*, at https://www.fda.gov/downloads/Drugs/Guidances/ucm073511.pdf; and
  - *Q10 Pharmaceutical Quality System*, at https://www.fda.gov/downloads/drugs/guidances/ucm073517.pdf.
- **CGMP Consultant Recommended:** Because you failed to correct repeat violations, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. We recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and evaluate the completion and effectiveness of corrective actions and preventive actions. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for resolving all deficiencies and systemic flaws to ensure ongoing CGMP compliance.

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IPA Innovation, Quality and Global Reach

February, 2019: WL CMS #558914 (Akorn, Inc.) (3)

4. What Does FDA Want – Special Paragraphs

- **Data Integrity Remediation – Expanded**
  - Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download.
  - We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.
  - In response to this letter, provide the following…

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October, 2018: WL 320-19-01 (Hanlim Pharm. Co. Ltd.)

4. What Does FDA Want – Standard Requests for **Aseptic Practices**

- Your plan to assure strict adherence to appropriate aseptic practices and cleanroom behaviors. Specify how your firm will ensure routine and effective supervisory oversight during manufacture of each batch. Also, describe the frequency of quality assurance oversight, such as audits, during aseptic processing and other operations.
- A thorough risk assessment that evaluates how poor aseptic technique and cleanroom behavior such as that observed during the inspection may have affected quality and sterility of your drugs.
- Comprehensive, independent identification of all contamination hazards specific to your aseptic processes, equipment, and facilities. Provide 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 preventive 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, control, maintenance, and personnel qualification.

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October, 2018: WL 320-19-01 (Hanlim Pharm. Co. Ltd.) (2)

4. What Does FDA Want – Special Paragraphs

- **Data Integrity Remediation – Short**
  - Your quality system does not adequately ensure the accuracy and integrity of data to support the safety, effectiveness, and quality of the drugs you manufacture. See FDA's guidance document Data Integrity and Compliance With Drug CGMP for guidance on establishing and following CGMP compliant data integrity practices at https://www.fda.gov/media/97005/download.
  - We acknowledge that you are using a consultant to audit your operation and assist in meeting FDA requirements.
  - In response to this letter, provide the following…
- **CGMP consultant recommended**
  - We note that you have retained a CGMP consultant. Based upon the nature of the violations we identified at your firm and because you failed to adequately correct repeat violations, we strongly recommend that your consultant is qualified as set forth in 21 CFR section 211.34, to assist your firm in meeting CGMP requirements. We also recommend that a qualified third party perform a comprehensive audit of your entire operation for CGMP compliance, and evaluate the sufficiency, and effectiveness of corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.
  - Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

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September, 2018: WL 320-18-73 (Lernapharm Inc.)

4. What Does FDA Want – Standard Requests for **Investigations**

- Your comprehensive investigations into the additional 18 batches potentially affected by debris on the sealing [redacted], including your CAPA and a plan to ensure its effectiveness. If these investigations reveal any substandard quality drug products, provide actions that you will take such as notifying customers and product recalls.
- An update on your root-cause evaluations and related CAPA for all complaints you received relating to non-integral containers (e.g., leaking containers, dried contents), with special emphasis on further mitigation of human factors associated with the manufacturing process, in-process checks, and final inspection.
- An improved process for risk assessment.
- Your updated assessment of patient hazards associated with loss of package integrity.
- A comprehensive, independent assessment of your overall system for investigations of deviations, atypical events, complaints, out-of-specification results, and failures. Your CAPA should include but not be limited to improvements in investigation competencies, root-cause analysis, remediation, written procedures, and quality unit oversight. Also, include your process for evaluating CAPA effectiveness.

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September, 2018: WL 320-18-73 (Lernapharm Inc.) (2)

4. What Does FDA Want – Standard Requests for **Stability**

- A full summary of stability data results for all batches tested, with each time interval, attributes tested, the testing methods used, and the written stability protocol that was followed. Include testing of all microbiological and chemical attributes, and any updated test data to determine whether the integrity of your container-closure systems (and products are sterile, as applicable) is maintained throughout the entire shelf life.
- A comprehensive assessment and CAPA to ensure the adequacy of your stability program. Your CAPA should include, but should not be limited to a remediated standard operating procedure (SOP) describing your stability program; stability-indicating methods; stability studies to support each drug product in its container-closure system before distribution is permitted; an ongoing program in which representative batches of each product are added each year to the program to determine if the shelf-life claim remains valid; and specific attributes to be tested at each station.

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September, 2018: WL 320-18-73 (Lernapharm Inc.) (3)

4. What Does FDA Want – Standard Requests for **Environmental Monitoring**

- frequency, location, and duration of sampling; sample size; and specific sampling equipment and techniques;
- action and alert limits for each location, and a description of its function and ISO classification;
- instructions regarding investigations of out-of-limit (OOL) environmental monitoring results; and
- identification of microorganisms detected in environmental monitoring samples. For example, all microorganisms recovered in the filling room should be routinely identified.
- Also provide environmental monitoring and bioburden monitoring data including:
- A list of all lots of sterile [redacted]produced by your firm since January 2015 and all bioburden tests performed. Annotate which lots were tested for bioburden and timing of each sample [redacted]sterilization or earlier in the process). Include all microbial count test results and state whether microbial identification was performed. If so, provide the identity of each microbe.
- A list of all environmental monitoring tests done for sterile [redacted]production since January 2015, date of the sample, location sampled, and the identity of all isolated organisms.
- Your bioburden monitoring and testing procedures.
- A list of any out-of-specification results from bioburden or environmental monitoring testing and all original results and related investigations (if any result was re-tested or invalidated).

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September, 2018: WL 320-18-73 (Lernapharm Inc.) (4)

4. What Does FDA Want – Special Paragraphs

- **Additional guidance on aseptic processing:** See FDA's guidance document, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, to help you meet the CGMP requirements when manufacturing sterile drugs using aseptic processing, at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070342.pdf.
- **CGMP consultant recommended**
  - Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34, to assist your firm in meeting CGMP requirements. We also recommend that the qualified consultant perform a comprehensive audit of your entire operation for CGMP compliance and evaluate the completion and effectiveness of corrective actions and preventive actions before you pursue resolution of your firm's compliance status with FDA.
  - Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

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Tools For Effective Responses to Form FDA 483 Observations & WL

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How to Structure the Responses

- May be responding to multiple health authorities for the same or several facilities and may have similar or different issues.
- FDA has not published guidance for industry on how to prepare responses to investigational observations and WL violations.
- Operating in a global environment – rely on advice for responding to inspection findings and post-inspection letters from colleagues in the U.K. Medicines and Healthcare Products Regulator Agency (MHRA).

  - https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/444569/Responding_to_inspection_findings_Oct_2013.pdf
  - https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/778086/Guidance_on_responding_to_a_post_inspection_letter_February_2019.pdf

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What Is The Critical Content?

- Can ascertain what FDA most likely needs to determine that a response is complete and adequate to resolve the issues from information in the public domain.
  - See https://hpm.com/wp-content/uploads/2006/01/FDLI-ARTICLE-RESPONDING-TO-483-OR-WARNING-LETTER.pdf .
- Use the standard requests and special paragraphs from *similar* WL – anticipate FDA responses and use as feedback for improving quality systems.
- A comprehensive response should demonstrate that:
  - ❖Any patient safety risk has been addressed.
  - ❖Observations and the root cause(s) have been addressed.
  - ❖Corrective actions have been taken for all affected products.
  - ❖Remediation of systemic issues that created the conditions leading to the CGMP lapse.
  - ❖For actions that cannot be completed within the time for a response - there is a plan addressing the observations, including timelines and deliverables.

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What Is The Critical Content? (2)

- To develop an effective response, consider taking the following steps:
  - Prepare to investigate the observation(s) or violations.
  - Conduct a comprehensive investigation.
    - ❖Identify the categories of the observations or violations (such as the six quality systems) and any trends.
    - ❖Conduct a risk assessment.
    - ❖Identify the root cause.
  - Remediate the problem: Implement a thorough CAPA
  - Conduct a CAPA effectiveness check.

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Extra Topic of Interest: Recent WL Trends in Cross-Contamination

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Dec., 2018: WL CMS #564286 (Hangzhou Guoguang Touring Commodity Co.,Ltd.)

- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/hangzhou-guoguang-touring-commodity-coltd-564286-12142018
- What was the charge? Your firm failed to establish and follow adequate written procedures for cleaning and maintenance of equipment **(21 CFR 211.67(b)).**
- Reason - You have not conducted adequate cleaning validation studies to demonstrate that your cleaning procedures for non-dedicated production equipment are adequate to prevent cross-contamination between the products manufactured at your facility. During our inspection, we observed that you manufacture several [redacted] over-the-counter (OTC) drug products, including [redacted], on shared equipment you use to manufacture nondrug products, including an [redacted] product.

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Dec., 2018: WL CMS #564286 (Hangzhou Guoguang Touring Commodity Co.,Ltd.) (2)

- FDA policy contained in two special paragraphs as part of the charge – not at the end of the WL:
  - It is *unacceptable, as a matter of CGMP*, to continue manufacturing drugs using the same equipment that you use to manufacture [redacted] products.
  - In response to this letter, *discontinue* manufacturing drugs and non-pharmaceuticals on shared equipment in your facility. If you intend to continue to manufacture both pharmaceutical and non-pharmaceutical products at your facility, provide a plan to show how you will separate the areas in which you will maintain dedicated manufacturing equipment for your pharmaceutical and [redacted] product manufacturing operations.

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April, 2018: WL CMS #540940 (Ei LLC)

- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/ei-llc-540940-04162018
- What was the charge? Your firm failed to maintain adequate separate defined areas necessary to prevent contamination or mix-up **(21 CFR 211.42(c)).**
- Reason - Your firm manufactured topical human drugs and several pesticides in the same building, using shared equipment.
- FDA policy contained in two special paragraphs as part of the charge – not at the end of the WL:
  - It is *unacceptable as a matter of CGMP* to continue manufacturing drugs using the same equipment that you use to manufacture pesticides or other non-pharmaceutical products due to the risk of cross-contamination.

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April, 2018: WL CMS #540940 (Ei LLC) (2)

- FDA policy contained in two special paragraphs as part of the charge – not at the end of the WL:
  - *If you intend to continue to manufacture both pharmaceutical and non-pharmaceutical products at your facility*, provide a plan to show how you will maintain adequately separated and dedicated manufacturing equipment for your pharmaceutical and pesticide manufacturing operations. In addition, provide an analysis of your results for testing additional human drugs for pesticides and include a risk assessment for all drugs you have previously produced on equipment also used for pesticide production. For each product, assess the risk of potential contamination due to the shared equipment, and provide your plans for addressing the product quality and patient safety risks for any product still in distribution within expiry, including potential recalls or market withdrawals.

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March, 2018: WL CMS #537663 (Labocont Industrial SRL)

- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/labocont-industrial-srl-537663-03092018
- What was the charge? Your firm failed to perform operations within specifically defined areas of adequate size and to have separate or defined areas or such other control systems necessary to prevent contamination or mix-ups **(21 CFR 211.42(c)).**
- Reason - Your firm manufactures [redacted] and non-[redacted] drug products in the same facility. For example, [redacted] and [redacted] are manufactured along with over-the-counter (OTC) [redacted] non-[redacted] drug products. Your firm does not completely and comprehensively separate [redacted] production facilities, which presents an unacceptable risk of [redacted] contamination in other drug products manufactured at your facility.
- FDA policy contained in two special paragraphs as part of the charge – not at the end of the WL:
  - It is *unacceptable as a matter of CGMP* to continue manufacturing drugs using the same equipment that you use to manufacture pesticides or other non-pharmaceutical products due to the risk of cross-contamination.

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March, 2018: WL CMS #537663 (Labocont Industrial SRL) (2)

- FDA policy contained in two special paragraphs as part of the charge – not at the end of the WL:
  - *Dedicate the facility to [redacted] production only.* We strongly urge you to dedicate the facility to [redacted] only production. It is unacceptable to produce any other products in the same physical facility. If you intend to choose this option, provide your timeline for implementation. Also, be advised that it is inappropriate for different classes of [redacted] to be manufactured in the same facility. Significantly, our inspection found that you are currently producing [redacted] and non-[redacted] or other markets within the same facility, rather than in separate dedicated facilities.
  - *Fully decontaminate the facility*. It is profoundly difficult to completely decontaminate a facility of [redacted] residues. If you intend to attempt decontamination so that your facility can resume solely non-[redacted] production, provide a comprehensive decontamination plan for the facility. Also, provide highly-sensitive methods to detect any [redacted] and [redacted] residues throughout the facility, and address all potential sources of cross-contamination of [redacted] into non- [redacted] drugs. You should not introduce any drug products into the U.S. supply chain until FDA determines that your proposed decontamination plan, methods, and procedures are adequate, thorough, comprehensively implemented, and verified via an FDA inspection.

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June, 2017: WL CMS #515029 (ChemRite CoPak, Inc.)

- https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/chemrite-copac-inc-515029-06292017
- What was the charge? Your firm failed to maintain adequate separate defined areas necessary to prevent contamination or mix-up **(21 CFR 211.42(c)).**
- Reasons:

  - You manufacture several over-the-counter (OTC) oral rinses and oral moisturizing drug products, including [redacted], [redacted]Mouth Moisturizer, and [redacted] Oral Solution, for your customer, [redacted] Products Inc. You manufacture these oral drug solutions using the same equipment that you use to manufacture numerous non-pharmaceutical materials in your facility, including an industrial car care product, [redacted] Polish and Sealant.
  - This car care product is paraffin-based and labeled as “Harmful or fatal if swallowed” and “Keep out of reach of children.” You also manufacture other toxic non-pharmaceutical industrial and automotive care products, such as leather treatments ([redacted] Leather Care, [redacted]Leather Lotion) and sealants ([redacted] Poly Sealant), using the same mixing tank and filling line you use for OTC oral drug products.

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June, 2017: WL CMS #515029 (ChemRite CoPak, Inc.) (2)

- FDA policy contained in two special paragraphs as part of the charge – not at the end of the WL:
  - The ingredients in your non-pharmaceutical products are extremely difficult to remove from manufacturing equipment, and could contaminate the drug products that you manufacture on shared equipment, such as the various oral solutions discussed above. It is *unacceptable as a matter of CGMP* to continue manufacturing drugs using the same equipment that you use to manufacture toxic industrial-grade car care products.
  - In response to this letter, *discontinue* manufacturing drugs on shared equipment in your facility. If you intend to continue to manufacture both pharmaceutical and non-pharmaceutical products at your facility, provide a plan to show how you will separate the areas in which you will maintain dedicated manufacturing equipment for your pharmaceutical manufacturing and industrial product manufacturing operations.

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Public Reactions & Questions Regarding FDA Policy

- Once the WL to ChemRite was published, there were various blogs and publications that reacted to the FDA policy in the WL and raised questions.
  - See this blog as an example - http://www.fdalawblog.net/2017/08/word-to-the-wise-drug-manufacturer-dont-use-your-manufacturing-equipment-to-produce-toxic-non-pharma/
- CGMP regulations for facilities and equipment at 21 CFR §§ 211.42(c) & 67(a) do not require use of dedicated facilities and equipment for other than penicillin and related-beta lactam drugs.
- FDA guidance on GCMP Q&A for equipment cleaning:
  - **What are the cleaning validation requirements for potent compounds (e.g., compounds that are cytotoxic, mutagenic, or have high pharmacologic activity), and is dedicated equipment required?**
  - Separation or dedication of equipment and facilities for the manufacture of potent compounds is not specifically required by CGMP regulations. However, manufacturers should identify drugs with such risks and define the controls necessary to eliminate risk of product cross-contamination in nondedicated equipment and facilities.

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Public Reactions & Questions Regarding FDA Policy (2)

- Use of mandatory language in a WL that is not a final FDA action and is not an order from a court.
- FDA expected to be given significant deference to define “current” good manufacturing practices.
- FDA can resort to using “import alerts” to detain multiple products from a single facility that appear to be adulterated for not meeting CGMP.
- Not just FDA issues that need to be considered in these situations – collateral risks:
  - Other regulatory agencies that could have jurisdiction and increase compliance complexity.
  - Civil liability for products liability and negligence.
  - Negative publicity.
  - If a company is publicly listed, market value and shareholder lawsuits.
  - Contract duties and conditions as a supplier or manufacturer.

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Recent Developments That Could Affect How FDA Conducts Enforcement Actions

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How Will FDA Manage Two New Executive Orders?

- The information in this section of the presentation is based largely on a blog that was recently published on the Parexel® regulatory portal.
- You can find the blog posted here - https://www.parexel.com/solutions/consulting/regulatory.

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How Will FDA Manage Two New Executive Orders? (2)

- On October 9, 2019 the President of the U.S. signed two executive orders related to how U.S. government agencies create and use guidance.
- You can find the two executive orders here:
  - https://www.federalregister.gov/documents/2019/10/15/2019-22623/promoting-the-rule-of-law-through-improved-agency-guidance-documents
  - https://www.federalregister.gov/documents/2019/10/15/2019-22624/promoting-the-rule-of-law-through-transparency-and-fairness-in-civil-administrative-enforcement-and

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How Will FDA Manage Two New Executive Orders? (3)

- What is an executive order?
  - An executive order is a signed, written, and published directive from the President of the United States that manages operations of the federal government.
  - An executive order has much of the same power as a federal law – like regulations issued by U.S. government agencies like the FDA.
  - Executive orders are not legislation; they require no approval from Congress, and Congress cannot simply overturn them. Congress may pass legislation that might make it difficult, or even impossible, to carry out the order, such as removing funding. Only a sitting U.S. President may overturn an existing executive order by issuing another executive order to that effect.

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How Will FDA Manage Two New Executive Orders? (4)

- The first order – *Promoting the Rule of Law Through Improved Agency Guidance Documents* – essentially directs government agencies to adopt good guidance practices. For the most part, the FDA has already enacted these good guidance practices that are outlined in the executive order through its implementation of the regulations at 21 CFR § 10.115.
- The second order – *Promoting the Rule of Law Through Transparency and Fairness in Civil Administrative Enforcement and Adjudication* – is more likely to affect the FDA's current approach to enforcement actions for drugs. There are two significant elements in this order that potentially affect how FDA can conduct enforcement actions.
  - When an agency takes an administrative enforcement action, engages in adjudication, or otherwise makes a determination that has legal consequence for a person, it must establish a violation of law by applying statutes or regulations. The agency may not treat noncompliance with a standard of conduct announced solely in a guidance document as itself a violation of applicable statutes or regulations (from Sec. 3 of the order - emphasis added).
  - Before an agency takes any action with respect to a particular person that has legal consequence for that person, including by issuing to such a person a no-action letter, notice of noncompliance, or other similar notice, the agency must afford that person an opportunity to be heard, in person or in writing, regarding the agency's proposed legal and factual determinations. The agency must respond in writing and articulate the basis for its action (from Sec. 6 of the order – emphasis added).

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How Will FDA Manage Two New Executive Orders? (5)

- Areas that could potentially be affected by the executive order:
  - WL for active pharmaceutical ingredients (API) – ICH Q7A.
  - Use of “import alerts” (detention without physical examination (DWPE)).
  - WL for compounded drugs – insanitary conditions guidance.
  - FDA referencing guidance documents in WL.
- How have other federal agencies been reacting to the executive order?
  - Similar to FDA, the US Environmental Protection Agency (EPA) creates, publishes and relies on guidance documents extensively.
  - The administrator of the EPA has stated that the orders contain important implications to U.S. EPA processes that we will need to think critically about to implement.
  - The EPA will be quickly creating two working groups to address interpreting and applying the orders.
  - Issues that the EPA will consider include proposals to allow industries the “opportunity to be heard” before taking an enforcement action.
- Waiting to hear from FDA about how it intends to address the orders.

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Thank you very much for your hospitality, time and attention!

Please ask questions!