

FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5	Document Number: III-05	Revision #: 02 Revision Date: 08/13/2019
Title: <p style="text-align: center;">Analysts on Inspection</p>		Page 1 of 29

Sections in This Document

1. Historical Background and the Law	1
2. Analysts on Inspection	3
2.1. Preparing for an Inspection	3
2.2. Starting an Inspection	5
2.3. Regulatory Notes and Exhibits	5
2.4. Inspections and Travel	6
2.5. Sample Collection	7
3. Types of Inspections	7
3.1. Food Inspections	8
3.2. Drug Inspections	11
3.2.1. General Areas (Chemistry and Microbiology Inspections)	11
3.3. Team Inspections versus Solo Contract Laboratory inspections	21
4. Establishment Inspection Reports	22
5. FDA-483 Objectionable Conditions and Practices	24
6. eNSpect	24
6.1. Operating as the Lead Investigator	25
6.2. Operating as Part of a Team Inspection	25
6.3. Writing FDA-483 Observations in eNSpect	25
6.4. Writing the Establishment Inspection Report in eNSpect	26
7. Computerized Systems and Electronic Records	26
8. Helpful References Pages on the Internet or Intranet	27
9. Document History	28
10. Change History	28
11. Attachments	29

1. Historical Background and the Law

FDA's primary duty is that of a public health agency charged with the protection of the health of American consumers with regard to the safety and efficacy of foods, drugs, cosmetics, biologics, medical devices and radiological products.

The Agency's statutory requirements, defined primarily by the Food, Drug, and Cosmetic Act, (FD&C Act) were promulgated to ensure that consumers are

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 2 of 29</p>

protected against unsafe products, and from the adverse health or economic consequences of false or misleading labeling. This is often accomplished by an inspection of the facility. FDA’s authority to conduct an establishment inspection is found under Section 704 of the Act:

<https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterVIIGeneralAuthority/default.htm>

SEC. 704. [374] *“employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (A) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (B) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein.*

A separate notice shall be given for each such inspection, but a notice shall not be required for each entry made during the period covered by the inspection. Each such inspection shall be commenced and completed with reasonable promptness.

Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgment, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health.”

21 Code of Federal Regulations (CFR) 113 and 21 CFR 114 requires commercial processors of LACF and acidified foods to maintain complete records of processing, production, and initial distribution of these food products. 21 CFR 108.35(h) and 21 CFR 108.25(g) provide that a commercial processor shall permit the inspection and copying of these records by duly authorized employees of the FDA.

<https://www.gpo.gov/fdsys/search/submitcitation.action;jsessionid=KFHBPYSN S8LVSW6Cz8mC9TPniQw1Q8jY8q109yW9TytmpGh9KLZF!-1869614850!1418187217?publication=CFR>. The Demand for Records (FDA 482a) must identify the specific records requested and must be signed by the

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume III Section 5</i></p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title: <p style="text-align: center;">Analysts on Inspection</p> </p>		<p style="text-align: center;">Page 3 of 29</p>

investigator. It should be noted that FDA inspections do not extend to financial data, sales data, other shipment data, and research data (other than data for drugs, antibiotics, and reporting).

2. Analysts on Inspection

During the course of an analyst's career with FDA, they will often be expected to participate in the inspection of FDA regulated firms. Analysts bring scientific expertise, knowledge, and other skills to an inspection team. Participation may include making and recording observations to evaluate the firm's processes, practices and conditions; reviewing the firm's records; asking questions of the firm's management or employees; collection of samples; and participation in the discussion during the close out meeting or exit interview with the firm's management. Often the analyst will assist in the preparation of sample collection reports, observations, and establishment inspection reports.

2.1. Preparing for an Inspection

- A. An analyst on a team inspection lends scientific support and technical expertise to the inspection team. The type of team inspection that an analyst will participate in depends upon their area of expertise and the type or complexity of inspection being performed. Chemists, microbiologists, biologists, entomologists, sanitarians, biochemists, organoleptic specialists, and engineers all play an important role in a team inspection.
- B. Prior to beginning a team inspection, preparation is key. Review the district files of the firm to be inspected and acquaint oneself with the firm's inspectional history, testing practices, and products. Review the previous Establishment Inspection Reports (EIRs) and FDA 483 items. Review the inspectional assignment in FACTS and note what Program Assignment Code (PAC) is listed in the assignment (this will enable the analyst to locate the corresponding Compliance Program). Meet with the Consumer Safety Officer (CSO) and other team members before beginning the inspection. Also, review any applicable Laws, Regulations, Compliance Programs, Compliance Policy Guides, and Inspectional Guidance documents relating to the type of team inspection being performed. Do not forget to read the Investigators Operational Manual (IOM). The IOM is the primary source of guidance regarding Agency policy and procedures for establishment inspections and sampling by field investigators and analysts. Knowing what the analyst role is, and what will be expected of each team member is crucial.
- C. To prepare for an inspection, an analyst will need to:

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 4 of 29</p>

1. Read the inspectional assignment to determine what is to be covered.
 2. Review the File Jacket for the previous inspection(s); note previous deficiencies and if there were corrective actions.
 3. Review previous EIRs and 483s.
 4. Review the assigned Compliance Program.
 5. Review the related sections of the CFR.
 6. Review associated Guidance Documents.
 7. Ensure sample supplies are present and in good condition if the inspection requires sample collections.
- A. Depending on the type of team inspection, general responsibilities may include reviewing analytical data from production, manufacturing or testing facilities; reviewing and evaluating test methods; and observing actual analytical testing or manufacturing being performed at the facility to assure that good manufacturing practices and good laboratory practices are being used. An analyst may need to evaluate whether laboratory equipment is properly calibrated or qualified. Also, an analyst may need to evaluate sanitation practices and environmental conditions that might affect safe product packaging and production.
- B. During the inspection, an analyst may be asked to collect samples. Sampling operations are carried out using techniques to ensure that the sample is representative of the lot; that the sample of the product is in the same condition as it was before sampling, and that the collection technique does not compromise the compliance status of the lot. The type of samples that may be collected include in-line samples, environmental samples, sanitation samples, water samples, finished product samples, as well as the various controls associated with these samples. Read the corresponding Compliance Program and the IOM if samples are to be collected. For microbiological inspections, sampling products using aseptic techniques is critical. Aseptic sampling techniques are used to assure that the microbial load of a product is not increased or introduced by a poor sampling procedure. The use of sterile sampling implements and containers, as well as a prescribed sampling protocol ensures proper collection.
- C. Do remember that during the inspection, safety is paramount. When conducting an inspection, or collecting a sample at a firm, make sure that the proper protective clothing and safety equipment are used. The analyst may need to wear a jumpsuit, lab coat, safety glasses, safety

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 5 of 29</p>

shoes, hard hat, hearing protection or respiratory protection. In a sterile drug facility, there may be precise gowning procedures. Guidance should be provided by the firm's management. The analyst can also contact an ORS Industrial Hygienist or ORS Safety and Occupational Health management and discuss any concerns either prior to or during the inspection. The analyst will also need to discuss with the inspectional team and the firm's management any allergies which may preclude participation in certain aspects of the inspection.

2.2. Starting an Inspection

- A. A FDA-482 Notice of Inspection is presented to the most responsible person upon entering a firm. Credentials are also displayed at this time. The analyst will be expected to display their FDA credentials. Securing official credentials through a supervisor may take 1-2 weeks and is done prior to going on inspection.
- B. In the case of an international inspection, only credentials are displayed since the Notice is not issued.
- C. Analysts must secure an official passport prior to overseas travel. Depending on the country, an official visa may also be needed for entry into the country.
- D. The investigator will usually give a brief synopsis of why the inspection is occurring. In the case of a directed or for-cause inspection, the investigator may be vague. Do NOT add to the investigator's comments unless discussed previously.

2.3. Regulatory Notes and Exhibits

- A. During the inspection, notes are expected to be recorded in accordance with Subchapter 2.1 Regulatory Notes of the IOM. This subchapter identifies what should be included and what should not be included in inspectional notes or diary notebook. Keep in mind these notes are considered part of the inspection and are subject to the Freedom of Information Action (FOIA). A return address should also be located on the notebook in case it is lost.
- B. The inspectional notes are factual based upon what was reviewed and observed during the inspection. The analyst may want to document product names, batch numbers reviewed, names and titles of people spoken to during the inspection and who provided information, SOP numbers of the methods reviewed, raw material, in-process or finished product testing reviewed (e.g., purity assays, dissolution results, objectionable microorganism plate counts) or, the systems reviewed (e.g., sampling, water system testing, or environmental monitoring).

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 6 of 29</p>

- C. Exhibits are any documents collected during an inspection which are included in the EIR as evidence of observations. Exhibits should contribute to the objective of the assignment and the clarity of the report. In some cases, exhibits may be physical materials that constitute evidence for establishing violative conditions. These types of exhibits are prepared and submitted under an INV sample number. In-plant photographs are exhibits as well; however, they are submitted under seal in a FDA-525 envelope as an exhibit to the EIR or with a documentary sample.
- D. During the inspection, it is best to collect photocopies of methods, results, standard operating procedures, schedules, etc. that may be used to assist in the description of a process or an objectionable condition. Documents not included in the report should be properly destroyed or shredded. Relate this practice to the firm at the time of collection. In the case of electronic file copies, the Division Office may have a policy addressing their disposal or the firm may request the return of the electronic files. Either way, state in the report how the electronic files were treated.
- E. The "Exhibits" section of the EIR contains a list of all exhibits cited in the EIR.
- F. Each exhibit is labeled with the following:
 - 1. Exhibit number,
 - 2. Name of the firm,
 - 3. Firm FEI number,
 - 4. Dates of the inspection,
 - 5. Initials of the team member(s) submitting the exhibit, and
 - 6. Number of pages in the exhibit.
- G. In the EIR, they are listed with their reference number and a title or description. The lead investigator decides how exhibits will be numbered (i.e., whether the analyst's exhibits will be included with those of the investigator and numbered sequentially or included in a separate appended report and numbered separately).

2.4. Inspections and Travel

- A. Travel is outlined in the IOM in Subchapter 1.2 (Travel) under CHAPTER 1 (ADMINISTRATION).

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title: <p style="text-align: center;">Analysts on Inspection</p> </p>		<p style="text-align: center;">Page 7 of 29</p>

- B. There are many instances when an analyst will be requested to travel outside of the local travel area or to another Division. In these instances, the analyst needs to follow the Division/ ORS policies. If planning to stay overnight, the analyst will need to have a Travel Authorization prepared and have it approved PRIOR to the start of the travel.
- C. For on the road inspections, a lap top computer can be a very helpful tool to have at the inspectional location. With a lap top computer, reports can be worked on in the evenings and will allow the analyst to contact various resources for assistance after-hours.

2.5. Sample Collection

Sampling is outlined in the IOM under the chapter “SAMPLING.” This chapter explains the step by step process for collecting samples. Refer to Chapter 4 (SAMPLING) for detailed instructions. It describes the types of samples typically collected during an inspection. A receipt for sample (FDA 484) is issued when collecting physical samples. This receipt is issued after the completion of the inspection but prior to leaving the premises. This process is clearly explained in sections 4.2.5 Receipt for Sample. In cases of documentary samples, there is usually a need for the issuance of an affidavit. Affidavits are explained in section 4.4.8 AFFIDAVITS. The form typically used is the FDA 463a. Affidavits are crucial since these documents are used to tie all the records collected to the objectionable conditions and show interstate transportation. Analysts who write affidavits should consult the Investigations or Compliance Branch for the proper style as well as review this section in the IOM.

3. Types of Inspections

An establishment inspection is a careful, critical, official examination of a facility to determine its compliance with laws administered by FDA. Inspections may be used to obtain evidence to support legal action when violations of the law are found or they may be directed to obtain information on new technologies, good commercial practices or data for establishing other regulations, etc. The kind and type of inspections conducted will normally be defined by a Center program or assignment. There are comprehensive and directed inspections. Comprehensive inspections direct coverage to everything in the firm subject to FDA jurisdiction while a directed inspection focuses on the areas described in the Center program or assignment.

The types of inspections most analysts find themselves on are directed inspections of food or drug firms. On occasion, analysts will accompany

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 8 of 29</p>

consumer safety officers on the inspection of cosmetics, medical devices, and animal feed firms.

3.1. Food Inspections

- A. The Food, Drug, and Cosmetic Act (FD&C Act) provides protection of the public from products that may be deleterious, are unclean or decomposed, or have been exposed to insanitary conditions that may contaminate the product with filth or may render it injurious to health. A food microbiologist, entomologist, chemist or sanitarian may participate in a team inspection of food manufacturers in order to evaluate and document insanitary conditions (e.g., filth and microbiological contamination), decomposition, adulteration with pesticides and industrial chemicals, or illegal use of color or food additives.
- B. There are specific current Good Manufacturing Practice (cGMP) regulations that must be followed by food processing facilities under 21 CFR Part 110 “Current Good Manufacturing Practice in Manufacturing, Packing or Holding Human Food”. Analysts need to review and become familiar with this section of the CFR. In addition, analysts need to assess whether the water being used in contact with the product (contact water) is safe. Processing water includes water that is used for post-harvest treatment of produce, such as washing, cooling, waxing, and product transport. Water can be a carrier of many microorganisms including pathogenic strains of *Escherichia coli*, *Salmonella*, *Vibrio cholerae*, *Shigella*, *Cryptosporidium parvum*, *Giardia lamblia*, *Cyclospora cayetanensis*, *Toxoplasma gondii*, and the Norwalk and Hepatitis A viruses. Even small amounts of contamination with some of these organisms can result in foodborne illness. Reusing processing water may result in the build-up of microbial loads, including undesirable pathogens from the crop.
- C. Good Manufacturing Practices (GMPs) for water used for food and food contact surfaces in processing facilities are in Title 21 of the Code of Federal Regulations (CFR), sections 110.37(a) and 110.80(a)(1). 21 CFR 110.19 provides an exemption from the requirements in 21 CFR part 110 for establishments engaged solely in the harvesting, storage, or distribution of raw agricultural commodities.
- D. The analyst needs to evaluate whether food contact services are cleaned and handled properly. Food contact surfaces may be sanitized by a process that is effective in destroying or substantially reducing the numbers of microorganisms of public health concern, as well as other undesirable microorganisms, without adversely affecting the quality of the involved product or its safety for the consumer.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 9 of 29</p>

- E. The analyst will also need to assure that the facility has proper precautions in place to reduce the risk for food contamination or cross contamination, personal protection is being used, proper handling of toxic compounds is being performed, and health conditions and pests are being addressed.
- F. Food sanitation team inspections may also involve an entomologist or food sanitarian. During a team inspection at a food warehouse, the entomologist or food sanitarian may be able to lend expertise in identifying or documenting insect infestation or rodent contamination of food products during warehouse storage. For example, documentation and identification of whole insects, excreta pellets, urine stains, insect damage, and insect and/or rodent gnawing will be needed to support certain regulatory actions.
- G. A microbiological inspection demands a thorough understanding of the critical factors associated with the production and testing of the product being inspected. During the inspection, a microbiologist needs to fully identify the likely sources and possible routes of microbiological contamination which includes but is not limited to the handling of the product and environmental conditions. The microbiologist will need to document temperature abuses and delays in processing steps that will affect the product, evaluate microbial testing of the incoming product component(s) or of the finished product(s), and focus on positive findings of pathogenic microorganisms; determine if equipment is constructed or covered to protect contents from dust and environmental contamination; determine what equipment is present in the laboratory and if it is usable for the purpose intended. If the firm uses a consulting laboratory, determine what tests are performed and how often. Review laboratory records for the period immediately preceding the inspection.
- H. One of the common types of team inspections a microbiologist may participate in are Low-acid canned food or Acidified food manufacturer inspections. The absence of oxygen, normal room temperature storage conditions, moisture and nutrients associated with low-acid foods favors growth of *Clostridium botulinum*. Failure to either destroy or control (by water activity or acidification) the germination and growth of spores of *Clostridium botulinum* because of improper manufacture, processing, or packing may result in the production of a toxin which causes the potentially fatal food poisoning known as botulism.
- I. Low-acid canned foods and Acidified foods are subject to all of the requirements under the Federal Food, Drug, and Cosmetic Act and the Fair Packaging and Labeling Act. These laws require that foods be safe,

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 10 of 29</p>

clean, and wholesome, and that labeling be honest and informative. The processing of Low-acid canned foods must comply with the requirements of the Good Manufacturing Practice regulations (21 CFR Part 113). The processing of Acidified foods must comply with the requirements of the Good Manufacturing Practice regulations (21 CFR Part 114).

- J. Sections 21 CFR 108 & 113 on Thermally Processed Low-Acid Foods Packaged in Hermetically Sealed Containers, and 21 CFR 114 Acidified Foods are of particular importance when conducting these types of inspections.
- K. Another type of food inspection is a HACCP inspection. FDA's Seafood Hazard Analysis Critical Control Point (HACCP) program is set forth in 21 CFR part 123. These regulations require processors of fish and fishery products to operate preventive control systems for human food safety that incorporate seven principles of HACCP. Processors must, among other things, establish "critical control points" in their operations where they can most effectively maintain the safety of their products, systematically monitor the operation of those critical control points to ensure that they are working as they should, and keep records of the results of that monitoring. Processors also must develop written HACCP plans that describe the details and operation of their HACCP systems. Each processor may tailor its HACCP system to meet its own circumstances.
- L. The regulations require processors to make their HACCP records and plans "for official review and copying at reasonable times" (§123.9 (c)). Finally, the regulations provide that fish and fishery products are adulterated under section 402(a) (4) of the Federal Food, Drug, and Cosmetic Act if their processor fails to have and implement a HACCP plan when one is called for, or otherwise fails to meet any of the requirements of the regulations, including allowing the official review of records (§123.6(g)).
- M. Another type of team inspection the analyst may participate in is a High-Risk Food inspection. High-Risk foods are foods that are susceptible to contamination by pathogenic organisms and that are essentially ready-to-eat; that is, they will not undergo a sufficient kill step by the preparer. Microbiologists are often asked to participate in cheese inspections. Some cheeses (primarily soft cheeses) have been linked to foodborne outbreaks and illnesses caused by Salmonella, Listeria monocytogenes, and Escherichia coli contamination. Consumption of Feta and Mexican-style soft cheese has been linked to a high rate of perinatal listeriosis.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume III Section 5</i></p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 11 of 29</p>

During the inspection, a microbiologist may be asked to review the testing of these pathogens.

3.2. Drug Inspections

There are several different types of drug inspections and each has a different focus. For example, a cGMP inspection determines if the laboratory is performing analytical testing in accordance with cGMPs. The scope of this type of inspection is broad and usually encompasses all product related operations. Pre-Approval inspections determine if the laboratory is performing analytical testing in accordance with cGMPs, human and animal drug application commitments, and the data submitted in the application is verified against the raw data. The scope of this type of inspection is narrow and focuses solely on operations which impact the drug product mentioned in the application. Post Approval Audit inspections provide continuing coverage of approved products.

However, there are areas common to these inspections. As a chemist or microbiologist participating in a team inspection, these common areas may be used as a starting point during the inspection.

3.2.1. General Areas (Chemistry and Microbiology Inspections)

The following areas are typically covered during all pharmaceutical inspections when applicable. These are considered the backbone of the pharmaceutical laboratory inspections. In addition, the United States Pharmacopoeia is useful source for information.

3.2.1.1. Accountability of Raw Materials and/or Samples

- A. Have an employee, preferably the person who actually works in this area and not management, explain the firm's receiving, sampling, assigning samples, and quarantine procedures.
- B. Visually examine the receiving area and storage rooms. Determine if the room is acceptable for the materials in storage or does the climate need to be controlled and if so, how. Examine the temperature control records.
- C. Review all pertinent Standard Operating Procedures (SOP) and compare with actual operations. Review physical records to determine compliance with the SOPs for this area.

3.2.1.2. Testing

- A. Examine methods with corresponding product specifications to determine acceptability. If a product specification is in question, discuss it with the review chemist or review microbiologist for the application.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 12 of 29</p>

Product specifications are a Center issue and cannot be placed on a FDA-483.

- B. With the aid of the Investigator, select a product and lot number(s). Review all analytical data associated with this product. This includes raw material testing, in-process testing, finished product testing, and stability testing. Check calculations (or spreadsheets), transcriptions, and reviewer's signatures for errors and discrepancies.
- C. Ask for and review the raw data and notebooks associated with each test. Compare the raw data to the summary documents.
- D. Review method validation records to determine adequacy (See Method Validation section for guidance). Determine if the method used in the microbiology or chemistry laboratory is the same as the method that was validated.
- E. Compare all analytical results with product specifications. Determine whether raw material or products with non-compliant test results were released, retested, or reworked.
- F. Examine written procedures for retesting of failed product (for example, assay failure or sterility failure) and compare with actual laboratory practice. Evaluate if the written procedure is complete and usable (See Out of Specification/Product Failure section).
- G. Ask to see all initial positive sterility test results. If a manufacturer of aseptically filled products has never found an initial positive sterility result, there may be a testing issue.
- H. Microbiological testing may include an identification of colonies or isolates found during the Total Aerobic Plate Count test or enrichment testing. Review these documents.
- I. If the method was validated at another site, review the method transfer documents to determine if the transfer was a success (see Method transfer section for guidance).
- J. For ancillary systems, select an audit period for evaluation of water system testing and environmental monitoring of controlled areas for sterile products.
- K. Review bacterial endotoxin, and bioburden testing data for parenterals, and any objectionable microorganism testing for non-sterile drugs. The amount of testing performed on non-sterile drugs will depend upon the product and its intended use. The significance of microorganisms in non-sterile pharmaceutical products should be evaluated in terms of the

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume III Section 5</i></p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 13 of 29</p>

use of the product, the nature of the product, and the potential hazard to the user.

- L. Media fill, environmental monitoring, sterility test results, and other data should be reviewed to assure the absence of slow growing organisms.
- M. Determine if raw materials are periodically retested to assure continued quality. Review the associated procedures to determine compliance.
- N. Determine if dehydrated media is being used for the preparation of media. Good practice includes the periodic challenge of prepared media.
- O. Review the methods being used for microorganism incubation to determine if they conform to those listed in approved or pending applications. Evaluate the time period used for sterility test sample incubation.

3.2.1.3. Standards/Controls

- A. Visually examine standard/controls storage conditions.
- B. Examine how indicator organisms are being stored.
- C. Review written procedures to determine how positive and negative controls are prepared. Good practice for such testing includes the use of known terminally sterilized or irradiated samples as a system control. Alternatively, vials or ampoules filled during media fills have also been used.
- D. Review the standard written procedures and compare with standard storage conditions and the use logs for compliance.
- E. Determine if the firm uses secondary or in-house standards. Evaluate whether the assay to determine potency and purity is complete and usable.
- F. Determine if the secondary or in-house standards are re-assayed periodically. Does the written procedure address how often this re-assay occurs? Is there sufficient data to determine if this re-test period is valid? Who performs the re-testing?
- G. Determine if the primary standard has expired.
- H. Determine how often volumetric solutions are standardized. Evaluate if this schedule is valid. Determine if commercially purchased standard solutions are standardized as well. Keep in mind that commercial standards solutions are not primary standards and need to be periodically re-standardized.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume III Section 5</i></p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 14 of 29</p>

- I. Review standardization logs or records for completeness and compare with the written procedure for compliance.

3.2.1.4. Equipment and Facilities

- A. Visually examine analytical equipment for proper maintenance and upkeep. Determine if the calibration/qualification status meets the SOP.
- B. Obtain a list of analytical equipment that is in use if possible.
- C. Review instrument written procedures and compare with maintenance and calibration/qualification records for compliance.
- D. Determine if the calibration/qualification written procedure is valid. Should the instrument be calibrated/qualified daily, weekly, monthly, quarterly, yearly? Is there data to support this schedule is followed? Does the procedure have specification limits, specific directions, and remedial action directions?
- E. Equipment should be evaluated with its intended use in mind. For example, dissolution apparatus dedicated to paddles, may not need to be calibrated with both paddles and baskets, and an autoclave used for a specified temperature range may not have to be calibrated at all temperature ranges.
- F. For sterile products, the USP states, "The facility for sterility testing should be such as to offer no greater a microbial challenge to the articles being tested than that of an aseptic processing production facility". If possible and feasible, the analyst should actually observe how sterility testing is being performed by the laboratory analysts. Proper design would, therefore, include a gowning area and pass-through airlock. Environmental monitoring and gowning should be equivalent to that used for manufacturing product.
- G. Begin the inspection with a review of microbiological analyses being conducted and inspect the plates and tubes of media being incubated.
- H. Inspect the autoclaves used for the sterilization of media.
- I. Inspect ovens used for pyrogenation and washers used for stoppers.

3.2.1.5. Stability

- A. Drug products are to remain potent throughout their shelf life. Therefore, the firm needs to be able to show that their product still meets assay and other specifications throughout its life. In order to do this, stability programs are set up and product is tested on a predetermined schedule to assure it is still a quality product. This is

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume III Section 5</i></p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 15 of 29</p>

also required by the cGMPs in 21 CFR 211.166(a). GMPs allow accelerated studies to be used to establish a tentative expiration date. However, real time stability studies are conducted at defined temperatures which reflect normal storage conditions. Stability should cover the physical, chemical, and microbial attributes of the drug substance. Validated stability indicating analytical procedures are to be used (See Stability Indicating Methods and Preservative Effectiveness Testing).

- B. For real time stability studies, representative samples from a minimum of three batches are stored at the labeled temperature (e.g. room, refrigerated, frozen) for a period at least as long as the proposed expiration date. The recommended testing schedule is quarterly the first year, semiannually the second year, and yearly thereafter; yearly testing is considered the minimum. Note that the firm's actual testing schedule may vary from this recommendation depending on the specifics of the product. The testing schedule will be defined by the stability protocol.
- C. Once a product is approved, firms are expected to maintain a continuing stability program by placing a representative sample from at least one batch a year in a room temperature stability program.
- D. Temperature, humidity, light, air/oxygen may need to be controlled and documented within the specifications set by the stability program protocol. The product is stored in the packaging container(s)/closure(s) intended for marketing. Product containers are stored in such a way so that the product is in contact with as much of the inner surface of the container as possible; for example, a bottle of syrup would be laid on its side or inverted so that the syrup is in contact with both the bottle and the bottle cap.
- E. For Active Pharmaceutical Ingredients, the retest date is the date after which a sample of the drug substance should be tested to ensure that the material is still potent for use. They are not required to have an expiration date.
- F. The following steps are taken:
 - 1. Visually examine the products in the stability chambers. Determine if the products are in the containers in which they will be marketed. Determine if the product is stored properly in the chamber. For example, liquids should be stored in both the upright and inverted positions.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 16 of 29</p>

2. Evaluate the temperature and humidity controls and determine if they will deliver the correct heat and moisture. Are the controls standardized with NIST traceable temperatures devices and is there sufficient documentation to support this?
3. Review stability written procedures and protocols and determine if the firm is in compliance.
4. Review stability testing records and determine whether stability tests are performed as scheduled using stability indicating methods (See Method Validation section). If scheduled pull dates were missed, verify the reasoning for this with related documentation.
5. For sterile products, an evaluation of final product stability at the specified expiration date should also be performed.

3.2.1.6. Personnel

- A. Obtain an organization chart for the firm. From this, determine the employees involved in lab work.
- B. Examine training records for compliance with written procedures.
- C. Examine employees' experience and training records. Review firm's procedures for employee qualifications for specific duties and evaluate whether employees have been properly qualified to perform the job duties you have observed for them.
- D. Ensure employees' workloads are doable.

3.2.1.7. Documentation

- A. Ensure analytical test, equipment calibrations, and sample accountability are thoroughly documented.
- B. Ensure analytical records are reviewed and signed off on by authorized personnel.
- C. Ensure all mark outs, crossovers, and errors are properly explained, initialed and dated in accordance with SOPs and GMPs.

3.2.1.8. Standard Operating Procedures (SOPs)/Written Procedures

- A. Examine laboratory SOPs and written procedures and evaluate for thoroughness and compliance with GMPs.
- B. Determine if SOPs are easily found by employees.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume III Section 5</i></p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 17 of 29</p>

C. Review implementation dates and sign-off dates. Determine if the SOP or written procedure that is to be used is actually being used by the laboratory analysts.

3.2.1.9. Method Validation, Stability Indicating Methods, and Preservative Effectiveness Testing

There are several guidance documents written about chemistry method validation. Note that some of these documents are still in draft form. Review of these documents is critical in order to gain an understanding of what method validation means and what the Agency's thinking is. The United States Pharmacopoeia also describes and defines the concept of method validation.

There are seven common threads throughout these documents: accuracy, linearity, range, precision, detection limit, quantitation limit, specificity, and ruggedness/robustness. Other factors listed in one or more of the documents include recovery, stability of solutions, and system suitability. Each factor is clearly explained in the references listed. Remember that all of these validation factors are not needed for each and every method. The amount of validation will depend on the type of method being validated and its intended use.

Table 1 Recommended Validation Characteristics of the Various Types of Tests

FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5	Document Number: III-05	Revision #: 02 Revision Date: 08/13/2019
Title: <p style="text-align: center;">Analysts on Inspection</p>		Page 18 of 29

Type of Tests / Characteristics	ID	Testing for Impurities		Assay Dissolution (Measurement Only), Content/Potency	Specific Tests
		Quantitative	Limit		
Accuracy	-	+	-	+	+ ⁴
Precision-Repeatability	-	+	-	+	+ ⁴
Precision-Intermediate Precision	-	+ ¹	-	+ ¹	+ ⁴
Specificity	+ ²	+	+	+ ⁵	+ ⁴
Detection Limit	-	- ³	+	-	-
Quantitation Limit	-	+	-	-	-
Linearity	-	+	-	+	-
Range	-	+	-	+	-
Robustness	-	+	- ³	+	+ ⁴

NOTE:

- Signifies that this characteristic is not normally evaluated.
- + Signifies that this characteristic is normally evaluated.
- ¹ In cases where reproducibility has been performed, intermediate precision is not needed.
- ² Lack of specificity for an analytical procedure may be compensated for by the addition of a second analytical procedure.
- ³ May be needed in some cases.
- ⁴ May not be needed in some cases.
- ⁵ Lack of specificity for an assay for release may be compensated for by impurities testing.

For microbiology methods, it would be virtually impossible to completely validate test procedures for every organism that may be objectionable, and methods need to be tailored to different types of products. It is essential to inactivate preservatives or inhibitory substances present in order to provide a better medium for damaged or slow growing cells. Other growth parameters include lowering the temperature and increasing the incubation time, which may provide a better survival condition for damaged or slow-growing cells.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume III Section 5</i></p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 19 of 29</p>

The selection of the correct neutralizing agents is largely dependent upon the preservative, inhibitory substance, and formulation of the product under evaluation. If there is growth in the enrichment broth, transfer to more selective agar media or an enrichment agar may be needed for subsequent identification. The method should optimize the recovery of all potential pathogens. There are instances when the product may enhance microbial growth and this may need to be determined for various assays.

Stability Indicating Methods and Preservative Effectiveness Testing

A stability-indicating assay accurately measures the active ingredients, without interference from degradation products, process impurities, excipients, or other potential impurities. This may be demonstrated by performing stress studies, also called forced degradation. Stress studies expose the product and/or drug substance to acid and base hydrolysis, thermal degradation, photolysis, oxidation etc. The stress studies should demonstrate that impurities and degradants from the active ingredient and drug product excipients do not interfere with the quantitation of the active ingredient. Drug product stress testing (forced degradation) may not be needed when the routes of degradation and the suitability of the analytical procedures can be determined through use of the following:

1. Data from stress testing of drug substance.
2. Reference materials for process impurities and degradants.
3. Data from accelerated and long-term studies on drug substance.
4. Data from accelerated and long-term studies on drug product.
5. Additional supportive information on the specificity of the analytical methods and on degradation pathways of the drug substance are found in literature sources.

Method Validation is also addressed in parts 211.160(a), 211.165 (e), 211.166 (a)(3) and 211.194(a)(2) of the GMPs. It is also addressed in various ICH (*The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use*) documents.

There are four basic microbial tests for finished product and stability samples.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 20 of 29</p>

1. Sterility Tests: For products such as sterile intravenous solutions and intrathecal injections.
2. Bacterial Endotoxin Tests (Limulus Amebocyte Lysate): Tests for the presence of endotoxins in injectable drug products and implanted medical devices.
3. Antimicrobial Effectiveness Tests: For products containing preservatives to inhibit the growth of microorganisms such as nasal and ophthalmic products.
4. Microbiological Examination of Nonsterile Products (formerly known as Microbial Limits Tests): For products that must be free of certain microorganisms listed in USP.

For sterile products, microbial preservative effectiveness testing needs to be performed during stability studies. This test is usually later replaced by chemical testing. It is important to note that for sterile products, container/closure integrity needs to be assessed not only at the beginning of the study but also at the end to demonstrate that the product remains sterile.

3.2.1.10. Method Transfer

Method transfer occurs when a validated method is transferred from one group, site, or company to another. There needs to be a Method Transfer protocol/plan/procedure in place. This protocol outlines the testing to occur, the roles of the two laboratories, and defines the acceptable values for the transfer to be accepted. During the inspection, the data from the transfer should be reviewed and compared to the protocol to determine if the data meets the acceptance criteria. Typical instances when method transfer occurs are from the Research and Development (R&D) laboratory to the Quality Control (QC) laboratory, Site A to Site B when a product line is moved, and Company X to Company Y when a product is purchased by another company.

3.2.1.11. Out of Specification (OOS) Results

During the course of analytical testing, there will be times when results are generated that do NOT meet product specifications. It is imperative that the firm has a procedure in place to handle these occurrences. During the inspection, an analyst needs to obtain a list of all batches which had an OOS result as well as a list of all failure investigations performed. It is important that when reviewing data, raw data is included in the review. Often passing results are obtained by averaging a passing result with an OOS result.

FDA regulations require that an investigation be conducted whenever an OOS test result is obtained. The purpose of the investigation is to determine the

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 21 of 29</p>

cause of the OOS. Even if a batch is rejected based on an OOS result, the investigation is needed to determine if the result is associated with other batches of the same drug product or other products. Batch rejection does not negate the need to perform the investigation. The regulations require that a written record of the investigation be made including the conclusions of the investigation and follow-up (21 CFR 211.192).

The FDA has published “Guidance for Industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production” to assist industry and FDA investigators and analysts when reviewing OOS investigations. The concepts mentioned in the guidance document apply to laboratory testing during the manufacture of active pharmaceutical ingredients, excipients, and other components and the testing of finished products to the extent that current good manufacturing practice (CGMP) regulations apply (21 CFR parts 210 and 211). The guidance discusses how to investigate suspect or OOS test results, including responsibilities of laboratory personnel, laboratory phase of the investigation, additional testing that may be needed, when to expand the investigation outside the laboratory, and the final evaluation of all test results.

3.3. Team Inspections versus Solo Contract Laboratory inspections

- A. Analysts that participate in inspections may be part of an Investigational Team consisting of Investigator(s) and possibly other analysts depending on the firm and focus of the inspection.
- B. As a team member, the analyst will be expected to follow the Investigations Operations Manual (IOM) and communicate with the lead investigator. The IOM can be found at <http://www.fda.gov/ICECI/Inspections/IOM/default.htm>. The electronic copy is the official version and should be referenced prior to performing an inspection.
- C. The lead investigator is ultimately responsible for the inspection. However, an analyst needs to make sure that he or she is also aware of the objectionable conditions that the other team members are finding. Communication between team members is important. Manufacturing cGMP violations may also result in laboratory violations. The analyst will be responsible for writing their part of the FDA-483 Observations, but the lead investigator may change the wording to follow his/her style. In many instances, it is a give and take situation. When the investigator is rewording the analyst’s observations, focus on whether the intent and meaning of the observation is the same. If the rewording changes the meaning or intent, clearly explain this to the investigator and works

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 22 of 29</p>

together to write the observation so all team members understand the objectionable condition.

D. If the analyst is acting as the lead investigator, the analyst should familiarize him or herself with the IOM. The analyst will need to issue the FDA-482 Notice of Inspection upon entering the inspection site. Issuance of the FDA-483 is clearly explained in the IOM. While performing a "solo" inspection, extremely violative conditions may be found. Consult with the local district office management to determine the course of action. Documentary samples and/or physical samples may need to be collected and an affidavit and/or receipt for the sample may need to be issued. Some districts may choose to send an investigator out for this part of the inspection or the analyst may be asked to do this on their own. If the analyst is to proceed alone, he or she should consult the IOM for the proper procedure and paperwork, as well as, with the local investigation staff, determine the best course of action.

E. For analysts participating in inspections, the following sections in the IOM are extremely helpful:

1. CHAPTER 5 - ESTABLISHMENT INSPECTION
2. Subchapter 5.1 Inspection Information
3. Subchapter 5.2 Inspection Procedures
4. Subchapter 5.3 Evidence Development
5. Subchapter 5.4 Food
6. Subchapter 5.5 Drugs
7. Subchapter 5.6 Devices
8. Subchapter 5.7 Biologics
9. Subchapter 5.8 Tobacco Products
10. Subchapter 5.9 Veterinary Medicine
11. Subchapter 5.10 Reporting

These subchapters identify the basics of an inspection. In the case of Drug Inspections, the IOM outlines the general areas covered during inspections.

4. Establishment Inspection Reports

A. Upon completion of an inspection, an Establishment Inspection Report (EIR) is written which details inspectional findings. Because analysts

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume III Section 5</i></p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 23 of 29</p>

may work independently of investigators during a team inspection, the analyst will submit a written report which is appended to the investigator's report. Excellent communication between the analyst and the investigator is the key during this type of inspection. There are some situations when the analyst and investigator are working so closely together that a separate report may not be needed, for example, the inspection of a contract laboratory. In this case, the analyst and investigator work out the details of how the report is to be written. All reports are prepared as stand-alone documents outside of FACTS. The establishment Inspection Report (EIR) is to:

1. Be factual, objective, and free of unsupportable conclusions.
 2. Be concise while covering all aspects of the inspection.
 3. Not include opinions about administrative or regulatory follow-up.
 4. Be written in the first person using the active voice.
 5. Be signed by all FDA and commissioned personnel participating in the inspection. See IOM section 5.1.2.5.1 when more than one FDA or commissioned person participated in the inspection.
- B. For an inspection that does not fall under the auspices of eNSpect, the analyst portion may consist of several sections depending on the scope and the length of the inspection. The IOM gives detailed guidance about the content of the EIR under section 5.10.4 – Narrative Report and 5.5.8- Drug Inspection Reports.
1. Analytical Narrative
 2. Objectionable Conditions
 3. Discussion with Management
 4. Exhibits

The narrative section details what was covered during the inspection (e.g. Samples/Batch review, Testing/Laboratory Operations, Laboratory Equipment Calibration/Qualification, Standards/Controls/Media/Reagents, Method Validation, OOS/Failure Investigations etc.). Depending on the scope, length of the inspection and significance of the finding, the analyst and the investigator may choose to include subheadings to clarify the report. The Objectionable findings/conditions section includes a detailed account of each objectionable condition (verbal and/or listed on the FDA 483) including a clear description of each, its impact on the product, batches or lots involved, and any relationship to other products or processes. Identify

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 24 of 29</p>

the responsible party for each violation. Report the discussion of all objectionable conditions from the daily inspection review and the discussion with management at the conclusion of the inspection. The "Discussion with Management" section of the report records management's response to objectionable conditions which are discussed during the exit interview. It also includes the names and titles of each person at exit interview. The investigator and analyst need to coordinate who writes this section and how it is written.

5. FDA-483 Objectionable Conditions and Practices

- A. Once an inspection is completed and before leaving the firm, an FDA-483 may be issued to the most responsible person at the site inspected. The FDA-483 itemizes all significant deviations from cGMPs. This may be prepared using eNSpect if applicable. If this is the case, please refer to the eNSpect section for additional guidance.
- B. When writing 483s as an analyst, observations should be:
 1. Significant and correlate to regulated products or process inspected.
 2. Directly linked to a cGMP regulation for inspections using eNSpect.
 3. Clear, accurate, and complete.
 4. Product names and lot numbers should be listed in the observation
 5. Listed in the order of significance.
 6. Legible if hand written.
 7. Related to the inspection. For example, failure to adhere to application commitments is an FDA-483 observation. However, product specifications are not a FDA-483 observation; and they should be discussed with the application Reviewer and addressed as a headquarters issue rather than a field issue.

6. eNSpect

- A. The eNSpect application is comprised of two components:
 1. eNSpect Web – a web-based application used mainly by those with a Supervisory role to create new inspection assignments, view assignments, and endorse the inspection.
 2. eNSpect Field Client – a desktop application loaded on the Investigator's laptop that can be used online or offline. The bulk of the Investigator's work is performed on the ENSPECT Field Client.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 25 of 29</p>

- B. The analyst should obtain access to eNSpect and ensure the inspection is associated with their laboratory in FACTS. This will ensure the analyst and the laboratory will receive time for the analysts' work conducted on the inspection.

6.1. Operating as the Lead Investigator

Lead Investigators must follow procedures detailed within the eNSpect guidance document found under ORA Applications (<http://inside.fda.gov:9003/it/Applications/ORAApplcations/default.htm>).

6.2. Operating as Part of a Team Inspection

- A. Specific roles are assigned for Inspectional Teams: Team Leader aka Lead and team members aka anyone other than the Lead participating in the inspection. Duties will be determined based on these roles.
- B. Teams can only be created once a Lead Investigator is assigned. A Supervisor can make team changes until the assignment is placed into progress within eNSpect. Once the assignment is changed to in progress, only the Lead Investigator can make team changes. Once the Lead creates the team and synchronizes with FDA network, each team member will receive DNS notification.
- C. This is needed in order for the analyst's name and title to appear in the signature block area of both the FDA-483 and the EIR, regardless of whether or not the analyst has a laptop.
- D. The analyst will find that communications between all members of the inspectional team are critical when using eNSpect, especially with respect to developing the FDA-483 and writing the EIR.

6.3. Writing FDA-483 Observations in eNSpect

- A. Once it has been established that eNSpect is going to be used on an inspection, the analyst is to write observations in eNSpect format regardless of whether the analyst has the application on their laptop. Each team member who has the eNSpect application can independently work on the FDA-483 on his or her own laptop. Independent team member observations shall be synchronized either at the end of each day or as determined by the Lead, thereby pushing their observations up to the FDA server. After all team members synchronize, the Lead will synchronize which brings all the observations into the Lead's computer. The team members can then synchronize again, which will download the latest version of the assignment showing all team members' observations.

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5</p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 26 of 29</p>

- B. Once the Lead completes their synchronization, this becomes the original 483 and is maintained on their computer. The Lead has the ability to edit all team members' work, while team members can only edit their own work. Team members working independently may duplicate citations; however, the Lead will determine final citations prior to completion of the 483. The Lead will Print and Issue Final Form 483. All team members present at time of issuance must electronically sign the 483 using PIV card.
- C. Please refer to eNSpect User Guide for details. If the analyst has difficulty identifying which citation(s) have been violated, ask the Lead Investigator for assistance. Analyst may be referred to a Supervisory Investigator or the Compliance Branch for assistance as well.
- D. If the analyst performs several inspections in a year, printing out the main or often used citations may be an advantage. It allows the analyst to read the citation on paper and discuss it with the investigator, whereas doing all on the computer can be more cumbersome at times.

6.4. Writing the Establishment Inspection Report in eNSpect

- A. Before the analyst begins writing the Establishment Inspection Report in eNSpect, the FDA-483 is signed and issued. All team members may work on the EIR independently; however, synchronization is required for information to be passed to the Lead. Unlike the 483, team members can only view their work and the Lead's – they will not see other team members' work.
- B. Team members can add attachments or exhibits; however, everyone should follow the same naming convention for consistency and should be discussed during the inspection. Once the EIR is in its final form, the Lead will finalize and synchronize. The Lead will then notify each team member independently for electronic signature. Once all signatures are obtained, the Lead will complete the Coverage and Conclusions page and the Endorsement page.
- C. Please refer to the eNSpect User Guide for details.
- D. Questions regarding eNSpect are best directed to the Lead Investigator.

7. Computerized Systems and Electronic Records

- A. Electronic records are records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under

<p style="text-align: center;">FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume III Section 5</i></p>	<p style="text-align: center;">Document Number: III-05</p>	<p style="text-align: center;">Revision #: 02 Revision Date: 08/13/2019</p>
<p>Title:</p> <p style="text-align: center;">Analysts on Inspection</p>		<p style="text-align: center;">Page 27 of 29</p>

requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

- B. Generally, analytical electronic records are generated on computerized systems, including, but not limited to chem-stations associated with analytical equipment such as HPLCs, GCs, FTIRs, and UVs. Computerized systems may also be connected to balances and other equipment where data is obtained. Computerized laboratory equipment should be evaluated during the inspection to determine if there is a data trail for the deletion and/or modification of data. The audit trail should have a time and date stamp and indicate what was modified and what the modifications were. If the software was written by the firm's technical support group, review the validation records and the challenges the firm performed. Determine if there have been any changes to the system or software since validation. If so, was a revalidation performed?
- C. Electronic Records and Signatures regulations apply to any record in electronic form that was created, modified, maintained, archived, retrieved, or transmitted under agency records requirements. These regulations also apply to any electronic record submitted to the agency.
- D. References:
 - 1. Code of Federal Regulations (CFR) Title 21 → Chapter I → Subchapter A → Part 11 Electronic Records/Electronic Signatures

8. Helpful References Pages on the Internet or Intranet

- A. ORA Inspection References
- B. ORA Inspections, Compliance, Enforcement, and Criminal Investigations (ICECI) Inspection References
- C. ORA Investigations Operations Manual (IOM)
- D. Electronic Code of Federal Regulations Title 21 Food and Drugs
- E. Inspections, Compliance, Enforcement, and Criminal Investigations (CDER) Inspection Guides
- F. Animal and Veterinary (CVM) Guidance for Industry
- G. CVM Bovine Spongiform Encephalopathy (BSE) Guidances
- H. CFSAN Food Guidance Documents

FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5	Document Number: III-05	Revision #: 02 Revision Date: 08/13/2019
Title: <p style="text-align: center;">Analysts on Inspection</p>		Page 28 of 29

- I. Vaccines, Blood & Biologics (CBER) Guidance, Compliance & Regulatory Information (Biologics)
 - J. CDRH Guidance Documents (Medical Devices and Radiation-Emitting Products)
 - K. Medical Devices (CDRH) Quality System (QS) Regulation/Medical Device Good Manufacturing Practices
 - L. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Official Website
 - M. Veterinary International Conference on Harmonization (VICH) Guidance Documents
 - N. Regulatory Information
 - O. Product Code Builder
 - P. eNSpect Guidance
- <http://inside.fda.gov:9003/it/Applications/ORAAApplications/default.htm>.

9. Document History

Revision #	Status* (D, I, R)	Date	Author Name and Title	Approving Official Name and Title
1.2	R	06/06/08	LMEB	LMEB
1.3	R	02/02/10	LMEB	LMEB
1.4	R	02/24/11	LMEB	LMEB
1.5	R	01/30/13	LMEB	LMEB
02	R	08/13/2019	LMEB	LMEB

* - D: Draft, I: Initial, R: Revision

10. Change History

Revision #	Change
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FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS ORA Laboratory Manual Volume III Section 5	Document Number: III-05	Revision #: 02 Revision Date: 08/13/2019
Title: <p style="text-align: center;">Analysts on Inspection</p>		Page 29 of 29

1.2	5.1, second website updated 5.3.3 IOM subchapter and links updated 5.6.2 section updated 5.8 Reference 2, 6, and 12 updated
1.3	5.2.1 – added bullet to list; deleted fourth sentence in paragraph 5 5.2.3 – revised last paragraph 5.3.1 – revised paragraph 7 5.3.2.1 – added last sentence to paragraph 1 5.4 – updated web link 5.7 – deleted last two bullets under References 5.8 – updated web links Footer – updated web link
1.4	5.3.3 – updated web link for the IOM 5.8 – removed CGMP Notes web link
1.5	Header – Division of Field Science changed to Office of Regulatory Science
02	Added procedures for eNSpect and removed content on TurboEIR. Clarified policy/procedures across the document.

11. Attachments

None