Sections in This Document

1. Introduction

ORA Laboratory Manual Volume II, ORA-LAB.5.10, defines the national procedures for reporting laboratory data. This document provides additional instructions for the preparation of analytical packages, including block-by-block directions for completing an Analyst Worksheet (FORM FDA 431 and FORM FDA 431a), and other associated documentation. It also describes laboratory protocols for recording observations and analytical findings (e.g., forms, notebooks, web applications, etc.)

2. Recording Analytical Information, Observations and Findings

2.1. General

The laboratory analyst records descriptive information pertaining to the sample, its handling in the laboratory, and analytical findings and observations on worksheets (e.g. FORM FDA 431, FORM FDA 431a), and in web applications, such as FACTS or Laboratory Information Management System (LIMS). General directions and considerations for completing these forms or electronic records include:

A. Sample information required for worksheets (hardcopy or electronic) are initiated upon receipt of the sample by the analyst. Blocks 1 through 9, and description of the container, labeling, codes, and product in Block 10 (FORM FDA 431), can be completed at this time.

B. Raw data and observations are recorded directly on the worksheets as acquired. For electronic data see section below on Electronically-entered Raw Data. When handwriting worksheets, the writing will be in permanent black or blue ink, and must be legible, neat, and of adequate size to be easily read and photocopied.

C. Do not write in the left margin on the front of the worksheet page and the right margin on the back. Information placed in these areas can be obscured or lost if worksheets are bound.

D. Do not erase, overwrite, or use correction fluid or tape to correct errors. For errors, draw a single line through the incorrect entry, write the

correct entry nearby, date and initial. Correction should be written clearly, without obscuring any other data, and in a manner, that avoids misinterpretation. Annotate the reason for the change, if it is not obvious. Always provide an explanation when discarding data.

E. Use only common abbreviations. The United States Pharmacopeia, General Notices, and the Official Methods of Analysis of AOAC INTERNATIONAL, Definition of Terms and Explanatory Notes, contain recognized scientific abbreviations. Clearly explain any abbreviations by defining them the first time they are used.

F. Measurements are made in metric units (e.g. cm, gm). Final results can be converted to the English system (e.g. oz, lb.) when applicable for comparison to label declarations, or the accepted convention for reporting the value.

G. A new FORM FDA 431 is started whenever a check or additional analysis is performed. Flag this new worksheet per part 3.3.2 of this document. These worksheets are completed following the instructions in part 3.3.2 with the following exceptions:

1. Blocks 8 and 9 need not be repeated, and can be left blank, or include the statement “see original analysis”.
2. Under Block 10 for items that remain the same, such as the description of the container, labeling, codes, and product, enter the statement “see original analysis”.

2.2. Analyst Worksheets

A variety of supplemental worksheets and related forms have been developed to support laboratory sample data recording and handling.

2.2.1. Basic Worksheets

The analyst worksheet (FORM FDA 431) and general continuation sheet (FORM FDA 431a) comprise the basic worksheets. Part 3.3.2 provides step-by-step instructions for preparing these worksheets. Computer templates of the FDA-431 and FDA-431a preserve the general format official forms. Management reviews and approves worksheet templates before use. Once worksheets are signed, they become part of the final analytical package.

2.2.2. Specialized Worksheets and Continuation Sheets

ORS harmonized worksheets are used when available.

2.2.3. Electronically-Entered Raw Data

Analysts may enter raw data and observations electronically using electronic worksheet templates or web applications in lieu of printed forms. Data and observations are recorded directly on these templates at the time they are observed. When data and observations are recorded electronically, laboratories take additional measures to protect integrity, which may include the following:

A. The analyst carefully reviews entries before saving and closing the file containing the entries.

B. Once raw data is entered electronically, and the completed worksheet file closed, changes to effect corrections to entries are now traceable (e.g. by initialed-and-dated strikeouts and additions).

C. The files containing raw data entries are identified in order to link them to the sample to maintain traceability. The files are protected (e.g. locked cells, password) from inadvertent change or loss.

D. Once the worksheet is signed, it becomes an official record. If corrections are necessary, they are made in accordance with 3.2.1 4. A new amended file is generated and the original file is retained to ensure traceability to corrections made.

2.2.4. Instrument-Generated Reports and Charts

When instrument-generated reports are included in an analytical package, the report should provide information needed to interpret its graphic, tabular, or computational output, such as: absorbency measurements, peak areas, retention times, wavelength maxima and other characteristics used in the generation of results. This should appear on each sheet of a report. The report should provide traceability to the instrument used, user (analyst), and sample.

The analytical package shall have available spectra or chromatograms that show the peak shapes, baseline noise, and other characteristics used in the generation of results.

In situations where an instrument produces a large number of spectra (e.g. GC/MS and FTIR/MS) and it is not practical to annotate them all, annotate those used to form analytical conclusions with the interpretive information contributing toward the final outcome.

2.3. Photographs, X-Rays, and Electronic Documentation

The analytical package may include photographs, x-rays, and electronic documentation to illustrate labeling, to assist in describing the product, or to

show an analytical finding. Because the size of an object may not be evident from the photograph or photocopy, it is recommended to include a ruler along with the object in the picture. When providing a photocopy with an enlargement or reduction, indicate the percent enlargement or reduction on the photocopy or mounting sheet. Photographs, x-rays, and electronic documentation must include sample identification, date, and initials.

2.4. FACTS (Field Accomplishments and Compliance Tracking System) or LIMS

Laboratory analysts enter analytical findings and observations following the analysis. The supervisor enters final conclusions and sample classification codes. Laboratory personnel will make every effort possible to ensure that they accurately enter data and errors are corrected as quickly as possible.

2.5. Notebooks

Analysts may keep bound notebooks to record non-sample specific data and observations. Sample-specific data and observations are recorded on the worksheets. The notebook is not to contain data, observations, and results applicable to identified samples. Keep in mind that sample background and other supporting information that may be contained in a notebook can be used as evidence in litigation.

2.5.1. Typical Uses of Notebooks

When an analyst elects to keep a notebook, it is bound, and the pages are hand-numbered or preprinted with numbers. Examples of the data that may be recorded in a notebook include the following:

A. calibration of weights, glassware and equipment; and

B. preparation and standardization of solutions and reagents

2.5.2. Maintaining the Notebook

General instructions for entering data are discussed in part 6.2.1(D).

3. Completing Worksheet and Continuation Sheet

3.1. General Information

An analyst initiates an analytical package (on FORM FDA 431,FORM FDA 431a or other approved worksheets) upon receipt from either sample custodian or transferred from another analyst.

3.2. Worksheet, FORM FDA 431

The FORM FDA 431 is completed as follows: (Supplemental to ORA Laboratory Manual, Volume II, ORA-LAB.5.10 Reporting Laboratory Data)

Flag: Indicate the appropriate "flag" in the top left margin of the worksheet to highlight the nature and significance of the sample for reviewers. The flag can indicate when other related reports are available or if the sample has a specific reporting need. This is an "optional" designation. Laboratories are to follow their local procedures for flags. A flag may be indicated for the following:

A. Check and Additional Analysis Samples;

B. Compliance and Surveillance Samples;

C. Complaint Samples;

D. Follow-up to Consumer Complaints, often denoted "F/U to CC";

E. Dealer Voluntarily Holding;

F. Audit Sample;

G. Split Samples; and

H. NDA and ANDA Samples

Block 1. Product: Specify the common or usual name of the product received for examination. When a label accompanies the product, the name entered is consistent with the name used on the product label. The name should also be consistent with information reported on the Collection Report (CR). If the product is a drug, include dosage form and strength. If the drug is a USP product, note this as part of the description.

Block 2. Sample Number: The assigned sample number.

Block 3. Sample Seals: Check one of the three blocks to show the seal condition upon sample receipt. Check "Intact" or "Broken" if the sample is sealed; or "None" if the sample is not sealed.

Block 4. Date Received: The date the analyst received the sample from the laboratory's Sample Custodian (or another analyst).

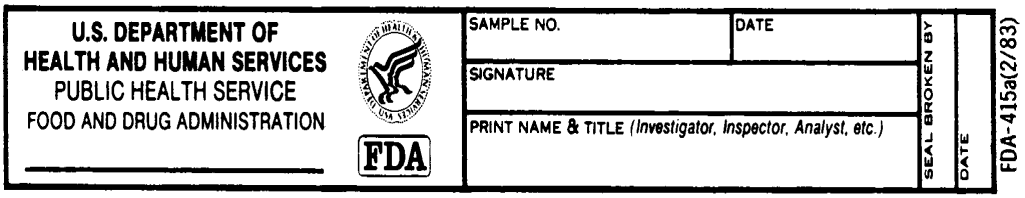
Block 5. Received From: The full name of person (first & last) from whom the sample was received, or location if the sample was obtained directly from storage.

Block 6. Laboratory: The common abbreviation for the laboratory (e.g. NFFL, KCL).

Block 7. Description of Sample: The complete description of the sample received. Quote the seal inscription (see next paragraph.) and note condition of the seal if damaged or broken. Quote the collector's identification on the sample, including sub-samples and sub-numbers. Specify the numbers and

describe the types of containers (e.g. clear plastic tray within a heat-sealed Mylar bag). Describe any abnormal sample conditions (e.g. torn, broken, not frozen). The worksheet "description of sample" contains only the basics for sample accountability and is consistent with the information on the Collection Report. Document any discrepancies or deviations found from the Collection Report on the worksheet pertaining to the collector's identification on the package and on the seal, and the number of subs collected.

Quote the official seal (FD-415a) exactly as written, including any mistakes and corrections. The seal is quoted in this order: sample number, date, and printed name (e.g., "X000001 1/1/00 Sidney H. Rogers"). When quoting a metal seal, quote both "U.S. Food and Drug" and the number on the seal. The seal quote is in quotation marks. The seal should be identical to the Collection Report, "Collector's Identification on Seal". If a discrepancy exists, the seal should not be broken, and the analyst should notify his or her supervisor. If a seal is completely illegible, the analyst should notify his or her supervisor and resolve seal problems with the investigator before proceeding.



Quote previously broken seal if present (e.g. from a previous analysis). Include "Seals Broken By", initials and date. Do not remove any official seals from sample unless absolutely necessary (e.g. to enter the sample or to maintain the chain of custody when there is no sample reserve). If a seal is removed, mount it on a sheet of heavy mounting paper and include with the analytical package as an attachment. Note the fact that the seal is attached and a brief description as to why the seal was removed on the worksheet in **Block 11**.

Other Information: Describe all sample items down to the container in contact with the product. Additionally, describe any standards and reagents included with the sample. If there is insufficient space in **Block 7**, reference location where information is continued. Note in **Block 7** any 702(b) portion of sample collected for the claimant.

Block 8. Net Contents: Record label declaration of net contents. When the net contents are listed in multiple units (i.e., both fluid ounces & milliliters) record both declarations. If the label declares both a "net" and a "drained" weight, then record only the net weight.

When applicable, indicate the number of sub-samples examined for net contents in the space to the left of "Units Examined". Also, report the average amount in units as declared on the label.

If there is no label or the label lacks a net contents declaration, check "Not Applicable." If the sample contains a labeled net contents and net contents was not determined, check "Not Determined".

Block 9. Labeling: The number of original labels, set, or copies submitted. Copies may be photocopies, photographs, handwritten copies "verified as true," etc. Copies are identified before copying by the analyst.

Check "None" if no product labels are being included with the analytical package. A "label" may be a single unit such as a paper label surrounding a can, or a set of separate units (e.g. Outer Product Labeling, Immediate Product Labeling, and Package Insert). A set is considered as one original.

Select and submit labeling that includes the sample collector's identification if available. This reinforces sample integrity when an original label cannot be submitted. The analyst identifies the original label and makes copies. If copies or photos of labels are submitted electronically, the original label must be retained.

At least one unit with the original label is retained "as is" for possible court use. Only under exceptional circumstances and with supervisory approval may a label be removed from a single container that represents the sample and be submitted with the worksheet.

For actionable samples, analytical packages include three (3) sets of labels and labeling or photocopies thereof. Include at least one set of the originals labeling, if available. Three sets of original labeling can be included as long as one unit with the original labeling is retained.

Handwritten or typed copies, which are "verified as true" by the original analyst and one additional analyst, may also be submitted. All originals and copies are identified with the FACTS sample number, date and analyst's initials.

For non-actionable samples, only one original or copy of the label and labeling need be submitted. In some cases, (e.g. survey samples and fresh produce submitted for pesticide residue analysis) submitting labels is not needed. This is at the discretion of the reviewing supervisor.

Attach labels to a sheet of mounting paper. If labeling is on two sides of submitted article, attach to mounting paper in a manner that allows both sides to be reviewed (e.g. staple just the top or side to the mounting paper). In the top right-hand corner of the mounting paper list the sample number, date, analyst's initials and the word "LABELING". On the mounting paper describe

what is being submitted (e.g. original cardboard box label, photocopy of bottle labeling, photograph of original tube) and include identification for example as Outer Product Labeling, Immediate Product Labeling, Package Insert. Assemble the labeling set copies as a set in the order packaged.

Block 10. Summary of Analysis: Summarize in concise and concrete language the following information under the headings and in the order listed:

A. Container;

B. Labeling;

C. Code;

D. Product;

E. Analysis (Purpose);

F. Method; and

G. Results.

Further clarification of directions for each of these items follows:

A. **Container:** Describe any commercial container in immediate contact with the product and any retail container(s) enclosing the immediate container. If a complete container or photo is submitted as labeling, do not describe it here, instead state that it is being submitted as labeling. Otherwise, record details as to the container's type, size, color, and closure(s). Color and closure may not be pertinent for some products but are always needed for drugs. Describe any abnormalities or unusual conditions associated with the container, such as opened can, abnormal can, evidence of leakage, or broken commercial seal. Do not describe in detail containers furnished by FDA and used by the collector, such as "Inspector's glass vials", "Whirl-Pak bag", or "Mason jar". For NDA and ANDA samples, describe only the primary product container. Secondary materials, such as standards and reagents, need not be described here, but should be referenced in Block 7: Description of Sample.

   Examples of container characteristics that should be described include the following:

   1. Shape (e.g. round, square);
   2. Color and Transparency (e.g. brown, clear, transparent, translucent, opaque);
   3. Material (e.g. glass, plastic, cardboard, Mylar);
   4. Type (e.g. can, bag, vial, bottle, syringe);

5. Closure (e.g. screw cap, septum seal, heat sealed); and
6. Dimensions in metric units (e.g. 6.5 cm high x 3.2 cm diameter).

B. **Labeling:** Describe labeling associated with the sample, including that found on retail cartons, inserts, direct printing, and wrappers attached to sample units. If labeling from the outer container enclosing the immediate container is submitted with the Collection Report or submitted as labeling, do not describe it here but state that this labeling has been submitted (e.g. copy of labeling from manufacturer's box).

Carefully review the label and labeling for correlation between analytical results and labeling statements, and for compliance with applicable labeling regulations. Discrepancies should be noted on the worksheet, and the reviewing supervisor should reflect these in the summary report.

C. **Code:** Quote sample codes and any product expiration date found on containers. Identify its type (e.g. embossed, ink stamped, perforated) and cite location. Do not record manufacturing codes (e.g. UPC, NDC). When there are units with differing codes in the sample, record all the codes and the number of units per code and correlate these with the sample collector's sub-sample numbers. When there is a discrepancy between the observed code(s) and the code(s) cited on the FACTS Collection Report, record the discrepancy on the worksheet. For certain types of samples (e.g. microwave ovens, TVs) a warehouse storage number, serial number, or model number may serve the same function as a product code.

D. **Product:** As applicable, provide a complete and accurate description of the product. Include color, shape, odor, general appearance and texture or consistency in lay language (e.g. frozen shrimp, whole frozen fish). When various sub-samples are raw materials, in-line products, finished products, and environmental samples, describe each in detail. Note any apparent abnormalities of the product (e.g. odor in aspirin bottles, broken tablets, discoloration, biological growth). A picture may be submitted as an attachment to further clarify the product description.

Do not use the word "normal" to describe a product itself. It may be used to qualify a characteristic of that product, such as "normal appearance".

In describing drugs in solid dosage form, the "Identification Guide for Solid Dosage Form", Journal of the American Medical Association (JAMA) provides descriptive terminology that may be helpful.

Some products, such as devices, may be difficult to describe. In such cases one may supplement a written description with a drawing or photograph whenever such an illustration will enhance the product description. Identify and attach the illustration and reference it in the written description.

E. **Analysis (Purpose):** Indicate the purpose of the analysis along with the number of units being tested. Note sub-numbers if applicable. Refer to the FACTS Collection Report block entitled "Reason For Collection" if there are questions regarding the purpose. Remember that subsequent reviewers may not be familiar with the details of the case or analysis; therefore, the rationale for an analysis is important. Reference compliance program, import alert, assignment, etc.

F. **Method:** For standard methods (e.g. United States Pharmacopeia, National Formulary, Official Methods of Analysis of AOAC INTERNATIONAL) or FDA "Official" methods (e.g. from compendia specified in the Food Drug and Cosmetic Act, Code of Federal Regulations and Compliance Programs, FDA manuals) identify a complete method reference, including edition, revision, or date and page number(s). For references accessed electronically, indicate "online" and date accessed. If applicable, record the section or chapter number, and date of any revision specific to section or chapter number. State any deviation and modifications made to the method. If selection and preparation of the analytical sample is not described in the method or applicable compliance program, describe this information in the analytical package.

   For approved non-standard and laboratory developed methods, the method used is referenced and kept on file with the analyzing laboratory for non-violative samples. For violative samples, the method used is attached to the analytical package as a memo of analysis. The worksheet references the memo as "attached memo of....". Number and include the memo itself as part of the attachment pages. For more than one sample, this reference is included with the lead sample and reference made to its location noted in the analytical packages for the other samples. Experimental work for validation studies is kept on file with the analyzing laboratory and available upon request

G. Results: Present analytical findings in a clear and concise manner to expedite interpretation of the results, especially by non-technical, non-scientific personnel.

Supply units (i.e., mg, oz, nm) for analytical data and express the data in the same units as those on the product label. Whenever possible, tabulate the analytical data.

If sub-samples with differing codes were individually examined, separately report the results for each code because regulatory action may be based on the results for a particular code exclusive of other codes.

Results reflect the correct number of significant figures as indicated by the analytical method.

Compare the analytical results with the label declarations, published tolerances and standards, regulatory action levels, manufacturer's specifications or other applicable criteria.

Record any discrepancies between analytical results and labeling statements or other criteria.

For analytical findings that are confirmed directly without a separate check analysis (e.g. confirmation of TLC spots that fade rapidly, identification of isolated filth elements, sensory confirmation) include a signed statement as to what was confirmed and by whom.

Block 11. Reserve Sample: When a reserve sample is retained, provide a description of it for accountability purposes. The amount of reserve remaining correlates with the difference between the amount received and the amount used in the analysis or provide an explanation for any discrepancy.

Quote the inscription on any new seal placed on the reserve sample. If the reserve sample is not returned to the sample custodian, record the place and condition of storage. When no reserve remains, state “NONE”, or “NO RESERVE”. Record the absence of a reserve in FACTS or in a LIMS.

When sending a portion of the sample to another party outside the laboratory, describe what was provided, how much, to whom, the date, how it was sealed, and a short explanation as to why the sample was sent.

If transferring all or a portion of the sample to an analyst within the laboratory indicate what was provided, to whom, the date, and a brief reason for the transfer.

Return to the sample custodian any developed x-rays or electronic media associated with the sample, which due to their bulk or storage-condition cannot be attached to the worksheet as part of the sample reserve. Otherwise submit such supporting documentation as attachments to the analytical report.

Block 12. Analyst Signature: If more than one analyst is involved in the analysis, the worksheet identifies the original analyst (who broke the seal) and the involvement of each individual who assisted with the analytical process.

The original analyst signs and dates Block 12a upon completing the 431 and checks the box if applicable.

Other analysts or technicians participating in the analysis also sign in Block 12. Each analyst should identify, initial and date their work as it appears elsewhere in the package.

If more than three individuals are involved in the analysis, the signatures can be continued on the FORM FDA 431a or on the back of the worksheet.

If an individual's signature is difficult to read, they need to also print their full name adjacent, above, or below to their signature.

With computer-generated worksheets, the names of the analysts involved may be already entered or typed in this block. In this instance, the analyst still needs to sign his or her name.

Block 13. Worksheet Check: A second analyst that is fully knowledgeable of the type of analysis performed or supervisor will review the worksheets and supporting records for technical quality (e.g. method suitability, accuracy of calculations, accuracy of data transferred from one section of the worksheet or attachment to another, completeness). The person who performs these checks will sign and date in this block.

Block 14. Date Reported: Following completion of the final worksheet review, the supervisor or reviewing official enters the date that the completed analytical package is classified.

3.3. Continuation Sheet, FORM FDA 431a

Use the "General Continuation Sheet" to continue information from Block 7, Block 10, Block 11, and to record other data and observations that will not fit on the first page of the worksheet (FORM FDA 431). The FORM FDA 431a or approved electronic template is also used to record raw analytical data, calculations; quality controls, calibrations, standardizations, and instruments or equipment used to complete the analysis, or reference to attachments, logbooks, or appropriate worksheets containing this information.

Complete the blocks of this form as follows:

A. **Product:** Enter product name identical to that found on the first page of the FORM FDA 431.

B. **Sample No.:** The FACTS assigned sample number. This number should be identical to that on the FORM FDA 431.

C. **Body:** The body on the FORM FDA 431a can be used for the following:

1. To continue information from the FORM FDA 431. When information is continued on the FORM FDA 431a, clearly indicate the block number, name and "continued". Reference where continued in original block on the FORM FDA 431.
2. To record raw analytical data, calculations, quality controls, calibrations, standardization, instrument operating parameters, and identification of instruments or equipment used to complete the analysis.
3. Use the following guidelines:
   a. Clearly annotate entries.
   b. Enter data in a clear, logical sequence. It is permissible to abbreviate, but there should be sufficient detail and identification for complete reconstruction and understanding of the data.
   c. When showing calculations, use the formulas given in the method whenever possible and explain any factors used in the calculation that are not evident in the method or from common knowledge.
   d. Provide traceability for the equipment and instruments used. This may include the name, model number, and instrument identification number. If this data is in an attachment, reference the location where this information is found.
   e. If the back of the sheet is used, enter the FACTS assigned sample number, date, analyst's initials and page number (i.e. Page X of Y) in the upper right-hand corner of each page on which an entry is made.

D. **Analyst:** The "lead" analyst signs his or her name in this block. When a computer-generated form already has the "lead" analyst's printed name in this block, he or she only needs to initial that entry.

E. **Page Number:** Consecutively number all the pages (i.e. Page X of Y).

3.4. Miscellaneous Data Entry

A. Unused areas of handwritten worksheets are marked by lining out. A diagonal line is placed through the entire empty space, initialed, and dated.

B. Unused data is lined out, initialed, dated, and state why the data was not used.

C. If data generated for a series of similar samples, each under a different sample number, are not completely recorded on or attached to each individual analytical package, reference the lead sample package containing the original data in each package.

   Examples of such data include a standard curve, the standardization of a solution, or TLC-plate observations.

   However, if a sample is violative, attach a copy of the original data to that package. Reference the sample number containing the original data on the violative package. Ensure the lead sample containing the original data stays with the violative package. A copy of the original data is not required to be attached to all the sample packages if all of the samples are violative. This reference is included with the lead sample and reference made to its location noted in the analytical packages for the other samples.

D. Include full name, source and lot number for all reference materials. List any pertinent preparation conditions (e.g. Drying at 105 □C for two hours, 2.34% water). For working standards include assay value, date, and a reference to where the assay data can be found.

E. If a computer application is used to generate results, list the name and date of latest revision (if it is not shown on the computer-generated data).

4. Types of Analyses

Different types of analyses may be conducted on samples. The type of analysis required is usually defined in the Compliance Program or Assignment. The types of analyses that are addressed in individual Compliance Programs and Assignments include the following:

A. Screening – used to detect the presence of a substance or class of substances at the level of interest and to filter large numbers of samples for potential non-compliant results. Results from a screening are usually considered estimates.

B. Confirmatory – used as a means to provide full or complementary information enabling the substance to be unequivocally identified and if necessary quantified. Methods that provide information on the chemical or DNA structure of the analyte or organism are considered confirmatory and do not always require a second determinative or check analysis.

C. Determinative (or Quantitative) analysis – used to determine the presence or concentration of an identified organism or analyte

D. Check Analysis – a separate and different analysis than the original analysis and used to confirm a finding

4.1. Check Analysis

The check analysis is performed to confirm a finding. The check analysis is performed by a standard method, validated, or FDA "Official" method. When such a procedure is not available, or is unsuitable for the analysis being performed, recovery data will be obtained to support validity of the results.

Requirements for check analyses are discussed below. These are not all-inclusive. There will be circumstances when the check is not required or, conversely, when it is judged necessary on a sample usually exempt from check analysis. Individual compliance programs and Compliance Policy Guides must be consulted for special requirements. When unusual circumstances exist, the appropriate center(s) must be consulted about the need for check analysis.

4.1.1. Check Analysis Requirements

Check analysis is necessary on violative regulatory samples, both domestic and import, and on violative samples that will be referred to a local, State, or Federal agency and that may form the basis for action by that agency.

Check analysis will be conducted by a second competent and qualified analyst and, when available, on a separate, intact portion of the product (e.g. intact food product. intact tablets, unopened vials or bottles of liquid products). In practice, there may be reasons for exceptions to this requirement:

A. When sample preparation instructions require compositing and comminuting or blending the entire sample (e.g. some pesticide or metal samples), the check analyst will analyze a second portion of the prepared composite. When comminution is not required for the entire composited sample, the check analyst will take a representative portion of the uncomminuted composite and subject it to the required additional preparation.

B. When program requirements do not provide a FDA reserve portion (e.g. certain medical devices, radiological health samples), where feasible, a second analyst may observe the original analyst's work or duplicate selected segments of the analysis on the same sample.

C. When the examination is for isolated filth and extraneous material, the check analyst need only examine elements isolated by the original analyst from a sufficient number of sub samples to be assured that the original analyst has reliably identified the elements.

D. When visual examinations for defective units of foods, drugs, or devices are conducted by an analyst, another analyst (usually one who is more experienced) confirms the defects.

E. For samples that traditionally do not have separate portions analyzed, such analysis is not truly a check analysis, rather, it is a confirmation of the original results. Such analyses include moisture and fat determinations on dairy product sub samples prepared by the original analyst, mold counts on sub samples prepared by the analyst if no FDA reserve portion is available, or organoleptic examination of sub samples analyzed by the original analyst if no FDA reserve is available and there are no instructions directing analysis of a separate intact portion.

When reagents, standards, and equipment are required in the analysis, the check analysis will be conducted independently of the original analysis. The check analyst must prepare the reagents and standards used or must demonstrate by reanalysis (e.g. volumetric solution), controls (e.g. media), or other objective evidence that those prepared by others have been prepared properly. When traceable reference standards exist (e.g. National Institute of Standards and Technology (NIST), USP), a reference standard from the current lot(s) must be used in the check analysis. When physical examinations are the issue and the same equipment must be used by the check analyst, the analyst must check the equipment to assure that it is calibrated and operating properly.

Check analysis of a sample may be requested of another FDA laboratory for a specific reason. Reasons for such a request include:

A. availability of a specialized analyst who is familiar with the method or the range of analytical responses exhibited by the commodity;

B. availability of specialized instrumentation; or

C. compliance programs may also state that check examinations are to be performed by specific FDA laboratories.

4.1.2. Check Analysis Not Required

Check analysis is not necessary in the following instances:

A. When certain types of samples are specifically exempted from the requirement for a check analysis by a compliance program or by the Compliance Policy Guides.

B. When check analysis of specific samples is waived by the Center.

C. When the original analysis is performed by a national or international expert, unless specifically called for by a program or by the Compliance

Policy Guides or when the method of analysis, instrumentation, or circumstances require check analysis by other experts. For field laboratories, this decision will be made by the Director, Office of Regulatory Science, in consultation with the laboratory director, and the appropriate Center compliance unit. Expert status shall be recorded on the analyst worksheet.

D. When the original analysis using a standard or FDA "Official" analytical method confirms the result of another government laboratory and personnel from that laboratory will so attest to the results.

E. The following types of out-of-compliance samples do not require check analysis:

1. Microbiological samples. Devices for sterility and samples analyzed for antibiotic potency using microbiological techniques do not require check analysis.
2. Samples originally examined for filth and extraneous material by an analyst recognized as a national or international expert in the particular micro analytical identification. Isolated material must be maintained with the reserve sample.
3. Exhibits of filth and extraneous material that have been isolated and submitted by the investigator or inspector and confirmed by a qualified analyst.
4. Samples for net weight determinations when initial weight was measured by the investigator or inspector and confirmed by a qualified analyst.
5. Samples proposed for regulatory action on the basis of labeling and the original analysis confirms the label declaration of ingredients.
6. Samples proposed for regulatory action where the violation is based on the qualitative identification by the laboratory of a prohibited substance which is present at "macro" (i.e. non-trace) level, using a highly-specific method such as mass spectrometry or infrared spectroscopy.

5. Assembling, Reviewing, and Approving the Analytical Package

5.1. Assembling the Analytical Package

The composition of the analytical package varies depending upon how the sample is handled or treated by the laboratory. Different classifications of the sample may result in a package lacking one or more of the records. Examples of this include samples that are classified as Class 5 which are ones collected

for analytical purposes but not examined or held for further action, and perishables that have arrived at the laboratory decomposed and cannot be analyzed. In this case, there will be no worksheets or analytical package; the sample will be closed in FACTS or LIMS.

The lead analyst is responsible for assembling the worksheet package.

Once the analysis is complete, records related to the sample are assembled for review as follows:

A. **Worksheets, Continuation Sheets (FORM FDA 431 and 431a), and Attachments** – Worksheets, continuation sheets, and attachments are assembled in a manner that effectively organizes and displays the analyst's findings.

   Page Numbering and Identification – Worksheets and continuation sheets compose the main sections of the analytical package and are numbered in consecutive order using a format showing the total number of pages (e.g. 1 of 6, 2 of 6. . .6 of 6.)

B. **Attachments** – Additional analytical records (e.g. instrument or computer-generated charts and data sheets, photographs, negatives, developed x-rays, electronic media, or photocopies) accumulated during the analytical phase of the sample examination attached as needed to support laboratory findings and conclusions.

   1. Each page of each attachment will be directly identified with the sample number, unique attachment number or letter, date, and initials of the analyst.
   2. The first page of each attachment is also titled, and attachments with multiple pages are numbered (e.g. 1 of 4, 2 of 4. . . 4 of 4).
   3. If the attachment is less than the size of a page or of awkward shape, the item may be mounted securely on heavy mounting paper. If mounting paper is used, it is also identified with the sample number, date, and the analyst's initials.
   4. The number of attachments included with the analytical package is listed as "Attachments A to ZZ" or "Attachments 1 to 99" in the bottom of block ten or in the bottom margin of the first page worksheet (FORM FDA 431).
   5. In situations where an instrument produces a large number of spectra (e.g. GC/MS and FTIR/MS) and it is not practical to attach them all to the package only those used to form analytical conclusions need be attached.

C. **Labels and Labeling** – Labels and labeling are separate from attachments and should not be identified as attachments in the analytical package. The number and types of labels and labeling included with a package are identified in Block 9 of the basic worksheet.

D. **Other Documents** – Optional

5.2. Reviewing and Approving the Analytical Package

After assembling the analytical package, the package is forwarded for review and approval.

A. Worksheet Check –A second qualified analyst or supervisor will review the package prior to it being forwarded to final reviewing official. The worksheet check reviewer inspects the package for accuracy and completeness and for errors or omissions. If issues are identified, the worksheet is returned for correction. Once the worksheet and supporting documentation is satisfactory, the reviewer will sign and date in Block 13 on the first page of the worksheet. If the worksheet check is not performed by the supervisor, the package is forwarded to the responsible supervisor for further review and classification.

B. Supervisor Review – Following the worksheet check, a supervisor reviews it for accuracy and completeness. If errors or omissions are discovered, it will be returned to the analyst for correction. Once the reviewing supervisor determines that the worksheet and supporting documentation are satisfactory, he or she completes Block 13 (if it is not already completed as a result of an analyst review), enters the date reported in Block 14, and enters their conclusions, related program assignment, and sample classification codes into FACTS or a LIMS.

C. Follow-Up Actions – If the data compiled by the analyst is insufficient or inadequate to determine the sample's compliance status, the responsible supervisor will contact the client (e.g. compliance officer, investigator, Center) to discuss and identify additional actions to resolve this situation.

5.3. Approving the Analytical Package and Reporting

Sample classifications are defined in the Glossary/Definitions section.

A. Approval of Class 1, 2, 4, and 5 Samples – Analytical packages for non-actionable samples will be approved by the responsible supervisor or designee. To indicate approval, the supervisor or designee will set the sample status in FACTS or a LIMS to "Completed".

B. Approval of Class 3 Samples – Analytical packages for actionable samples are approved by the laboratory director or designee.

The responsible supervisor will enter their conclusion(s) and sample classification code(s) into FACTS or a LIMS application when they find the package to be satisfactory. This supervisor will then set the status in FACTS or a LIMS to "Ready for the Laboratory Director's Review" or equivalent status in a LIMS and forward the package to the director or designee.

The laboratory director or designee reviews both the analytical package and recommended conclusions in FACTS or a LIMS. If the director or designee is not satisfied with the package or the FACTS or a LIMS summary, the package is returned to the responsible supervisor for corrections, changes, or additional testing. Once the director or designee finds the analytical package and FACTS or a LIMS input satisfactory, they will indicate their approval by setting the sample status in FACTS or a LIMS to "Completed".

5.4. Reporting Results

5.4.1. Reporting Microbiological Results

Report microbiological results in sample summary as indicated below:

A. Salmonella – No Salmonella spp. was detected in two composites analyzed.

B. Salmonella – Salmonella sp. was detected in one of two composites analyzed.

C. EHEC – No Enterohaemorrhagic Escherichia coli (EHEC) or STEC was detected in ten subs analyzed individually.

D. Listeria – No Listeria spp. was detected in two composites analyzed.

E. Listeria monocytogenes was detected in one of two composites analyzed.

F. Shigella – No Shigella spp. was detected in two composites analyzed.

NOTE: In the applied method section for Salmonella, Listeria, and Shigella testing, record "not speciated" under the Spcs Code.

5.4.2. Reporting Chemical Results

Report Chemical results as indicated below:

A. Results less than the Limit of Detection (LOD) or Method Detection Limit (MDL) – report as less than LOD or MDL and include the detection limit concentration.

B. Results between the LOD or MDL and the Limit of Quantitation (LOQ) – report the concentration and include the detection limit and quantitation limit concentration.

C. Results above the LOQ, report the sample concentration.

5.4.3. Reporting presumptive positive results or Cannot Rule Out (CRO)

When initial testing or screening indicate the possibility that the analyte or organism in question is present. Additional analysis is required to confirm the presence, absence or concentration.

6. Abbreviated Recording and Reporting of Findings for Surveillance Samples

ORA Laboratory Manual, Volume II, ORA-LAB.5.10, describes additional information on abbreviated reporting.

7. Consumer Complaint Letters

A complainant is to be informed of FDA's findings when a sample is examined. When the examination is completed (or if no examination is made), an inquiry is made to determine if the consumer wishes the sample returned.

There may be rare occasions when an intact complaint sample serves as the basis for legal actions. On these occasions, the compliance branch is consulted before an offer to return the remaining sample is made.

A letter is sent to the complainant advising the individual of the general nature of the findings. When additional interpretation is indicated, an explanation of the findings is included. If an examination has not been made, the complainant is informed and given the reason(s). Do not offer to return the sample if it is needed for FDA regulatory purposes or if it has been purchased from the complainant.

Sufficient copies of the consumer complaint letter must be provided for distribution to:

A. the complainant (original); and

B. the home division and collecting division, if different from the examining division (1 copy each); and

C. the analyzing laboratory (1 copy).

The letter to the complainant is sent by certified mail, return receipt requested, to establish a clear record of the transaction. If the complainant requests the sample, the sample is returned, and an appropriate record maintained. Complaint samples are held for at least thirty days from the time the letter is

sent. If sample return is not requested by the complainant during this period, the sample may be destroyed.

Cosmetic injury complaint reports will be handled by the Center for Food Safety and Applied Nutrition.

8. Glossary/Definitions

A. Analytical Package – A collection of printed records designed to provide a complete account of laboratory's analytical efforts and related findings and conclusions.

B. Attachments (to an Analytical Package) – Broken seals, instrument generated charts, chromatograms and spectra, contractor provided data, computer printouts, standard curves, photographs, x-rays, exhibits, photocopies are to support laboratory findings and conclusions.

C. Claimant's Portion – This is the portion of a sample, normally referred to as a 702(b) sample, that is retained by the laboratory in its original condition for examination by any person named on the label of the article, or the owner thereof, or their attorney or agent per the requirements of Section 702(b) of the FD&C Act and 21 CFR 2.10.

D. Labels or Labeling – Labels or labeling is commercially printed material that describes the contents of a sample package and is found in association with the product. Labels or labeling include carton labeling, bottle labels, all inserts, product packaging, promotional materials, photographs or photocopies of original label, or verified handwritten copies. Labels or labeling is often referred to as Outer Container Labeling, Immediate Container Labeling, and Package Insert. Labels or labeling is comprehensively defined in the FD&C Act, Sections 201(k) and 201(m).

E. Sample Classifications – Samples are assigned by laboratory supervisors to classes based upon whether they are considered "regulatory (classes 1, 2, 3, & 5)" or "non-regulatory (class 4)" in nature, and the results of the laboratory's examination.

   1. Class #1 (In Compliance) – The sample meets established standards (CFR, USP, etc.) or policy guides in the absence of standards.

   2. Class #2 (Regulatory Action Not Established/Defined):

a. the sample fails to meet established standards, but may meet policy guides;

b. in the absence of standard guides, results may or may not be applicable for regulatory actions because of the level or significance of the results but may still have implications for public health; For example, detection of Listeria species other than Listeria monocytogenes; acidified canned foods (ACD) where the process is not known; detection of Shiga Toxin E. coli (STEC)s; other examples include Potency Results that are borderline and the product is not close to expiration date; and Health Hazard Evaluations performed by the Center.

c. sample results may indicate the need for investigatory, compliance, and/or policy follow-up or further laboratory analysis. For example, 1) the laboratory identified a color which was permitted as a dye and not as a "lake" and the difference between the two forms could not be determined analytically; 2) Whole Genome Sequencing (WGS) for further pathogen characterization, data analysis and epidemiological considerations.

3. Class #3 (Adverse Findings) – The sample fails to meet established standards and policy guides; or the results, in the absence of standards and guides, are of a level or significance to support a recommendation for regulatory action. This classification is also used for documentary samples, exhibits or other types of samples which are being held without analysis for evidence in regulatory proceedings.

4. Class #4 (No Classification Needed) – The sample is not classified because of the type of examination or reason for analysis makes classification meaningless. Examples include survey samples where one sample consists of multiple products or where there is no documentation to support regulatory action. These include "Total Diet Samples" and samples examined for another regulatory agency that has responsibility for classifying the sample, or samples used in research or collaborative studies, response to consumer complaints or petition validation projects.

   Note: As noted in Section 5.3, the distinctions between Lab Classifications 1, 2, 4 and 5 samples and Lab Class 3 samples center around whether the analytical packages relate to non-actionable versus actionable packages. Since WGS result is generally supportive to previous actionable results, it is counter-

intuitive to continue to use LC4 for these types of analytical packages.

5. Class #5 (Sample Shipping and Collection Problems) – The sample is rendered unusable for analysis due to shipping of collection reasons, such as broken containers, improper collection, sample not collected. For other reasons, such as PAC codes, incorrect servicing laboratory, laboratory problems, the information is corrected in FACTS or a LIMS or the sample is properly transferred to another servicing laboratory in FACTS or a LIMS.

F. Regulatory Samples – All samples collected for regulatory analysis. Samples received from cooperating agencies may be regulatory or for information purposes only. They are to be handled the same as FDA samples. The following samples may be exceptions:

1. Survey samples for gathering information only. The design of the survey may not permit regulatory action (e.g. no 702(b) portion, insufficient units analyzed, multiple manufacturers under one sample number).
2. Samples collected to gather authentic data (e.g. food standards).
3. Samples designated as laboratory quality assurance samples.

G. Responsible Supervisor – The laboratory's branch or section level supervisor with primary responsibility for the sample being examined.

H. Standard Method and FDA "Official" Method – A method that is published by international, regional or national standards-writing bodies; by reputable technical organizations; in legal references; and FDA published methods. FDA "official" methods are those in compendia specified in the FD&C Act and prescribed in the CFR and methods in applications and petitions that have official status are included. These methods include those in the United States Pharmacopeia, National Formulary, Homeopathic Pharmacopeia of the United States, Official Methods of Analysis of AOAC INTERNATIONAL or any supplement of any of them, American Public Health Association (APHA) Compendium of Methods for the Microbiological Examination of Foods, FDA compliance programs, the Pesticide Analytical Manual (PAM), the Food Additives Analytical Manual, the Food Chemicals Codex, FDA Bacteriological Analytical Manual (BAM), FDA Macroanalytical Procedures Manual (MPM), and ORA Laboratory Information Bulletins (LIBs) that are included in compliance programs and special assignments.

9. References

A. ISO/IEC 17025:2017, General requirements for the competence of testing and calibration laboratories. Section 7.8.

B. AOAC International Guidelines for Laboratories Performing Microbiological and Chemical Analysis of Food, Dietary Supplements, and Pharmaceuticals – An Aid to Interpretation of ISO/IEC 17025:2017; August 2018.

C. LIMS User's Manual

10. Document History

Revision #	Status* (D, I, R)	Date	Author Name and Title	Approving Official Name and Title
1.3	R	03/23/05	LMEB	LMEB
1.4	R	12/06/06	LMEB	LMEB
1.5	R	08/15/08	LMEB	LMEB
1.6	R	02/02/10	LMEB	LMEB
1.7	R	07/20/10	LMEB	LMEB
1.8	R	02/06/12	LMEB	LMEB
1.9	R	01/29/13	LMEB	LMEB
2.0	R	05/02/14	LMEB	LMEB
03	R	06/06/2019	LMEB	LMEB

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

11. Change History

Revision #	Change
1.4	3.3.2, **Block 9. Labeling**: - added term "set"; defined "label" and set in first paragraph; added identification examples and assembly of labeling sets to last paragraph. 3.3.2 **Block 10. Summary of Analysis**: - moved second sentence from **Container:** to first paragraph of **Labeling:** 3.9 Changed from Document History to Document/Change History
1.5	3.4.2.2 Added f.
1.6	3.2.1 b. – corrected reference from 3.2.2.2 to 3.2.2.3 3.2.2.3 d. – corrected reference from 3.2.1 c. to 3.2.1 d. 3.2.5 – deleted reference to ORA Laboratory Manual, Volume V 3.5.3 – added "designee" to paragraph 3.6 – added reference to ORA-LAB.5.10, Section H.2. Footer - updated
1.7	3.3.3 Added "to complete the analysis, or reference to attachments, logbooks, or appropriate worksheets containing this information" to first paragraph. 3.5.1 and 3.8 Added "photocopies" as examples of attachments
1.8	3.3.2 Block 7 – added "from the Collection Report: in last sentence 3.3.2 Labeling – revised second sentence in second paragraph 3.4 – Title changed to Types of Analysis 3.4.1 – heading changed to Types; added bullets on Screening, Confirmatory, and Determinative 3.5.3 – added last section on reporting results 3.8 – revised Class #5 definition
1.9	Header – Division of Field Science changed to Office of Regulatory Science 3.4.2.2 c. – Division of Field Science changed to Office of Regulatory Science

Revision #	Change
2.0	Contents: 3.2.5 – added Laboratory Information System Contents: 3.9 – changed to References Contents: 3.10 – now Document Change History 3.1 – changed FACTS system to "web application, such as FACTS or LIMS" 3.2.1 – revised first paragraph 3.2.1 a. – added "Handwritten" 3.2.1 b. – added "or web application" 3.2.2.1 – added last sentence 3.2.2.3 – added "or web application" 3.2.2.3 c. – added "or electronically" 3.2.2.3 d. – added "or LIMS generated PDF file" 3.2.3 – revised second paragraph 3.2.5 – added references to LIMS 3.3.1 – added "or enters information into the web application" 3.3.2 – minor changes made to grammar 3.3.2 Block 6 – deleted District 3.3.2 Block 7 – added to last sentence 3.3.2 Block 9 – added to last sentence of first bullet on retaining original label 3.3.2 Block 10 Containers – added "or photo" 3.3.2 Block 10 Labeling – revised 3.3.2 Block 11 – added "or LIMS" 3.3.4 – added "handwritten" to first bullet 3.5.1 – added reference to LIMS at end of first paragraph & Attachments first bullet 3.5.2 – added reference to LIMS to Supervisor Review 3.5.3 – added reference to LIMS 3.8 – added reference to LIMS in definition of Lab Class 5 3.9 – added references
03	Revisions made as needed to align this procedure with new ISO/IEC 17025 and AOAC requirements. Revision to formatting and policy clarifications were also made.

12. Attachments

None