

FOOD AND DRUG ADMINISTRATION OFFICE OF REGULATORY AFFAIRS <i>ORA Laboratory Manual Volume I</i>	Document Number: ORA-LAB-QM	Revision #: 03 Revision Date: 08/13/2019
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1. Introduction

This Office of Regulatory Affairs (ORA) Laboratory Manual of Quality Policies (hereafter referred to as Volume I) has been prepared to meet the requirements for laboratory accreditation of the International Organization for Standardization/International Electrotechnical Commission (ISO/IEC 17025:2017).

2. Controlled Distribution of the Quality Manual

The Office of Regulatory Science (ORS) is responsible for maintaining the official master copy of the ORA Laboratory Manual which contains the ORA Laboratory Quality Manual. This Manual consists of Volume I, ORA Laboratory Manual of Management Requirements and Volume II, ISO 17025:2017 ORS Laboratory Procedures. The ORA Laboratory Manual also includes operational procedures and training in Vol III and Vol IV respectively. General distribution of this manual is accomplished using a computer network. Biennial review is coordinated by the Office of Regulatory Science.

3. Quality Policy Statement

ORA’s mission statement states “ORA protects consumers and enhances public health by maximizing compliance of FDA regulated products and minimizing risk associated with those products”. ORS laboratories are

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committed to providing testing that meets both the needs of the customers and the requirements of ISO/IEC 17025:2017 and to continually improve the effectiveness of the management system. Testing results are reported within stated limits of accuracy, precision, and detection limits as described in the methods used for analysis.

3.1. Management System Objectives

- A. The primary objective of the management system established by ORS laboratories is to assure the accuracy and precision of laboratory results so that they will be reliable, interpretable, repeatable, and defensible. Data quality objectives are described in the terms of:
 - 1. accuracy,
 - 2. precision,
 - 3. detection and quantitation limits,
 - 4. timeliness, and
 - 5. comparability.
- B. The second objective is to establish and maintain national and international recognition through compatibility with the requirements of relevant standards.
- C. Third, strive to meet or exceed the customer's needs and expectations.
- D. Fourth, maintain ORS laboratories' reputation for quality by fostering continuous process improvement and problem prevention.

These objectives are considered as part of the reviews performed by management.

3.2. Management System Awareness and Implementation

The management system documents and test methods are included as training elements in the laboratory's training program addressed in the laboratory training procedure. This ensures that staff is familiar with quality documentation and implement the quality policies and procedures in their work. See ORA Laboratory Manual, Volume II, ORA-LAB.5.2 Personnel Training and Competency Management.

4. General Requirements

4.1. Impartiality

- 4.1.1. To avoid conflicts of interest, pressures, and influences, FDA employees are familiar with and observe the Standards of Ethical Conduct. These principles of ethics can be found at **FDA Division of Ethics and Integrity**.

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- 4.1.2. Laboratory management is committed to sustaining impartiality of all personnel by enforcing existing FDA policies and requirements on ethics that were implemented to ensure impartiality in the agency's work.

The FDA provides several means to ensure impartiality of its employees, such as the HHS 520 Request for Approval of Outside Activity and OGE 450 Confidential Financial Disclosure Report Filer forms which are filled out annually and reviewed by the **FDA Division of Ethics and Integrity** to identify potential risks in relationships, ownership, finances, contracts, etc. that may impact personnel's neutrality regarding FDA related activities. In addition, a monthly list of significantly regulated organizations is distributed for review in keeping with 18 USC § 208 prohibiting personal and substantial participation in matters that have direct and predictable effect on their financial interests.

The Office of Government Ethics (OGE) also requires one hour of ethics training annually. Training is provided on ethics rules, regulations and integrity to help employees avoid placing themselves in a conflict of interest situation. An employee who performs laboratory testing performs and documents a demonstration of competence as prescribed in Volume I, Subsection 6.2.

- 4.1.3. Risks to impartiality are continuously reviewed and eliminated or minimized to ensure there is no compromise to the objectivity of staff engaged in laboratory activities. Employees are familiar with and observe the Standards of Ethical Conduct. Executive Order 12674, issued in 1989 and modified in 1990 by Executive Order 12731, states fourteen general principles that broadly define the obligations of public service. Two core concepts are embodied in these principles: (a) Employees shall not use public office for private gain, (b) and employees shall act impartially and not give preferential treatment to any private organization or individual.
- 4.1.4. Risks to impartiality may be identified during required routine disclosures by employees or during audits. When laboratory employees or processes pose a risk to impartiality, an assessment is made of the nature of the risk and appropriate corrective actions are taken by the laboratory and/or the designated agency authority.

4.2. Confidentiality

- 4.2.1. All FDA staff sign a Form FDA 2096 upon entry to duty. This form certifies their agreement to abide with 5 USC § 552a(1) the Privacy Act and 21 USC § 331 The Trade Secret Act. Contract employees are required to sign FDA FORM 3398 Commitment to Protect Non-Public Information Employee

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Agreement upon entry to duty. This form certifies their agreement to abide with 21 U.S.C. 331(j), 21 U.S.C 360j(c), and 18 U.S.C 1905. Confidentiality requirements are included in purchasing agreements, as needed, with vendors performing work in areas where laboratory work is performed.

- 4.2.2. ORS laboratories do not release confidential information to external parties. ORA's Office of Strategic Planning and Operational Planning, Division of Information Management Disclosure Policy manages ORA's information disclosure functions.
- 4.2.3. Reports of information and data are transmitted and filed in accordance with official policies, directives, and notices of the department and the agency. Most reports are only transmitted internally within the agency, except as required by law or regulation. Information is released only to the customer or designated representative. Field Management Directive (FMD) No. 147, Procedure for Release of Analytical Results Pursuant to Section 704 (d), provides guidance for reporting analytical results to an external customer.
- 4.2.4. FDA facilities are controlled-access buildings to further ensure protection of data. Names and purpose of all non-FDA visitors are provided to security prior to planned visits. Additional department policies are in place for visitors from other countries. Visitors are continuously escorted by FDA representatives and allowed only in areas approved by mandated security protocols in place to ensure no customer or federal information is compromised. Additionally, employees sign commitments to properly keep and use confidential information obtained or witnessed during their duties.

5. Structural Requirements

5.1. Laboratory as Legal Entity

The Food and Drug Administration (FDA) is a government agency under the Department of Health and Human Services (DHHS). The agency is required to follow the federal regulations in 21 CFR, 29 CFR, 40 CFR, 49 CFR, the FD&C Act and PHS Act.) ORS laboratories are legally responsible for all activities within their operations.

5.2. Management Responsible for Laboratory

The Office of Regulatory Affairs Associate Commissioner is responsible for establishing the organization's commitment to the management system, implementing it, and delegating responsibility for its accomplishment.

The Director of the Office of Regulatory Science is responsible for issuing policy and procedures for the ORS laboratories and monitoring their

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implementation.

Laboratory management, analysts, and quality managers are responsible for ensuring that analytical activities meet the requirements of the agency, its customers, and regulations in 21 Code of Federal Regulations (CFR), 29 CFR, Part 1910.1450, 40 CFR, Parts 260-264, 49 CFR, Parts 171-173 and the Food, Drug and Cosmetic (FD&C) Act. In addition, each person involved in the generation of data is part of the management system.

5.3. Scope of Accredited Laboratory Activities

Laboratory activities encompass all processes from the review of vendors for external products and services to sample, equipment, supply, and data handling and reporting within the laboratory. All ORS laboratories have documented training, proficiency, and method validation and verification programs in place. To ensure consistency in these processes controlled, approved documents are maintained to provide guidance in all processes and records retained to recreate processes, if needed. These also provide the basis to evaluate risks and improvements where gaps are identified through nonconformances, complaints, and annual management review of the inputs and outputs of operations.

5.4. Laboratory Requirements

The intent of ORA is to operate testing laboratories per the following requirements:

- A. FDA policies and procedures,
- B. ISO/IEC 17025:2017,
- C. Customer contracts (workplan),
- D. ORA compliance programs and assignments,
- E. Federal and State laws and regulations, and
- F. Accreditation registrar requirements.

ORS laboratories operate permanent facilities across the United States and Puerto Rico at the locations identified in the Staff Manual Guides (SMG), 1121.92 Office of Medical Products and Specialty Laboratory Operations and 1121.93 Office of Food and Feed Laboratory Operations.

5.5. Laboratory Organizational Structure and Procedures

- 5.5.1. The regulatory laboratories are a part of the Office of Regulatory Affairs, FDA and are identified in SMG 1121.9 series. The organization and the relationship among the laboratory staff is reflected in the laboratory's organizational chart maintained by the laboratory. These charts provide

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relationships between management, technical operations, and support personnel.

- 5.5.2. The laboratory has managerial staff with the authority to discharge their duties as reflected in the prepared job descriptions by the laboratory. This authority includes the implementation, maintenance, and improvement of the management system. Management authorities are defined in government classification standards found on the U.S. Office of Personnel Management website.

Job responsibilities for laboratory employees are documented in the management system procedures and operating instructions. Position descriptions are maintained by the Office of Human Resources (OHR).

- 5.5.3. The laboratory management system is outlined in the following documents:
- A. Quality manual,
 - B. Written procedures,
 - C. Work Instructions,
 - D. References, and
 - E. Forms and records.

This management system is established to address the requirements in ISO/IEC 17025:2017. Each entity establishes and maintains documents per the procedure for document control. The quality policy and quality objectives for ORS laboratories are included in Volume 1, section 3. The documents listed above are accessible to all personnel and are included in the laboratory's training program.

5.6. Personnel Responsibilities and Authority

Laboratory personnel are aware of their roles and contributions in the management system and of its objectives through regularly scheduled training provided by the quality staff. Laboratory personnel irrespective of other responsibilities have the authority and resources to carry out their duties.

- 5.6.1. General roles and responsibilities for ORS laboratory personnel are summarized as follows:

- F. Quality System Manager
 - 1. Ensures that the management system is established, implemented, and maintained in conformance with the requirements of ISO/IEC 17025:2017.
 - 2. Advocates and coordinates quality improvements to the

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management system.

G. Responsible Managers (technical management)

1. Oversee technical functions.
2. Ensure compliance with the requirements of ISO/IEC 17025:2017.
3. Ensure management system procedures, applicable standards, specifications, and regulations are followed.
4. Ensure that qualified, skilled, and trained personnel and other resources are available.
5. Ensure that products and services satisfy customer requirements.

H. Analysts and support staff

1. Ensure the quality of their work.
2. Operate in conformance with the requirements of the management system.

5.6.2. All laboratory employees have the authority and are encouraged to identify and report deviations from the management system or procedures for laboratory activities.

5.6.3. All laboratory employees contribute toward initiation of actions to minimize such deviations or provide input toward improvement to the system. These actions are monitored and reviewed by laboratory management.

5.6.4. The laboratory Quality System Manager (QSM) is responsible for monitoring the laboratory's management system and reporting its performance and any need for improvement to laboratory management.

Laboratory Management is responsible for the technical operations of the laboratory. Resources for training, laboratory methods, measurement traceability, and purchasing are described in other sections of this Volume and in relevant FDA Division of Ethics and Integrity.

Qualified laboratory personnel are assigned to serve in the absence of key managerial personnel, such as Laboratory Director, Quality System Manager, and Supervisors to maintain unbroken continuation of operations. In addition the laboratory has an active and executable contingency plan for the Continuity of Operations (COOP) in place with effectiveness drills enacted at least once each year.

5.7. Communication and Integrity of the Management System

5.7.1. Effective communication from management occurs through, but is not

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limited to, memos, newsletters, electronic presentations, emails, or verbally to laboratory personnel regarding the effectiveness of the management system and the importance of meeting customer, statutory, and regulatory requirements

- 5.7.2. The management system process and procedures as defined in this manual maintain the integrity of the management system when changes such as a change in the structure of the organization or management, or a change in a policy or procedure are made.

6. Resource Requirements

6.1. General

Personnel, facilities, equipment, systems and support services necessary for the management and performance of laboratory activities are evaluated and put in place to ensure defensible data and conformity to the requirements of ISO/IEC 17025:2017 General requirements for the competence of testing and calibration laboratories.

The sections following below address the factors affecting the correctness and reliability of the tests performed by a laboratory. These factors include contributions from:

- A. Personnel (ORA Laboratory Manual, Volume II, ORA-LAB.5.2 Personnel Training and Competency Management),
- B. Facilities and environmental conditions (ORA Laboratory Manual, Volume II, ORA-LAB.5.3 Facilities and Environmental Conditions),
- C. Equipment (ORA Laboratory Manual, Volume II, ORA-LAB.5.5 Equipment),
- D. Metrological traceability (ORA Laboratory Manual, Volume II, ORA-LAB.5.4.5 Methods, Method Verification and Validation; ORA-LAB.5.6 Measurement Traceability), and
- E. Externally provided products and services (ORA Laboratory Manual, Volume II, ORA-LAB.4.6 Purchasing and Receipt)

The procedures listed in each section address these factors.

6.2. Personnel

6.2.1. Personnel

All laboratory personnel that could influence laboratory activities act impartially, are competent, and perform their work according to the laboratory's management system. These positions include, but are not limited to: analysts,

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supervisors and managers, laboratory support staff, sample custodians, and administrative management staff.

6.2.2. **Competence Requirements**

Competence is based on education, experience, demonstrated skills, and training. Staff records contain the documentation of personnel education, qualification, experience, technical knowledge, skills, and training for the position held.

Skills of personnel are based upon demonstration of competence. Competency requirements for each function influencing the results of laboratory activities are documented in the laboratory's training documents. This demonstration is to be completed successfully before laboratory personnel generate data independently. The effectiveness of personnel training is documented in, but not limited to management reviews, internal audits, external assessments, proficiency testing, and performance evaluations.

6.2.3. **Personnel Competence**

Laboratory management ensures that laboratory personnel have the competence to perform their duties and to evaluate the significance of deviations.

Trainees undergo a training program in accordance with the laboratory's training documents and ORA Office of Training, Education and Development (OTED) standards. Trainees perform procedures when training and competency has been demonstrated. The documented demonstration of competence is an exercise that the trainee performs independent of supervision. The trainee is considered competent after the specified criteria have been successfully met.

6.2.4. **Communication of Duties, Responsibilities and Authorities**

Job duties, responsibilities and authorities for laboratory employees are documented in the management system procedures and operating instructions.

Position descriptions are maintained by the Office of Human Resources(OHR). The laboratory maintains active job descriptions for managerial, technical, and key support personnel involved in laboratory activities. Job descriptions are established based on current duties and technologies utilized.

The laboratory employees involved in laboratory activities have access to consensus standards, instrument manufacturers' manuals, and laboratory procedures for reference.

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Effective communication from management occurs through, but not limited to, memos, newsletters, electronic presentations, emails, or verbally to laboratory personnel regarding the effectiveness of the management system.

6.2.5. Personnel Procedures

- A. The procedure for determining competence requirements are defined in the laboratory's documents and ORA-LAB.5.2 Personnel Training and Competency Management.
- B. The Food and Drug Administration's, Office of Human Resources establishes the hiring procedures for the agency. FDA OHR SOP 300-07 *Category Rating* describes the selection procedures.
- C. The individual and management are jointly responsible for the setting, the pursuit, and achievement of educational goals for professional advancement. The annual performance evaluation process can be used by the individual to discuss career advancement and training possibilities. By using this process, individuals can identify areas of study and request training oriented towards the attainment of their goals. Procedures for employee career development are described in SMG 3120.1, Staff Development and Training, and FDA Supervisor's Desk Reference, Chapter 8, Training and Development.

Training needs are identified in accordance with the analyst's discipline (e.g. Chemist, Microbiologist) and FDA ORA/OTED standards. In-house training is conducted per laboratory's training procedure. Present and anticipated tasks of the laboratory are addressed in the planning of special training modules.

The management system documents and test methods are included as training elements in the laboratory's training program addressed in the laboratory training procedure. This ensures that staff is familiar with quality documentation and implement the quality policies and procedures in their work.

- D. The laboratory utilizes the skills and talent of both full-time employees and contract personnel. The requirements of the management system are administered equally to both categories. No differentiation is made between the two categories of workers. Supervision, training, and competence are documented for all technical and key support personnel.

Supervisors are designated, and trainees do not perform regulatory work until competent as per the laboratory training program. Procedures for supervision of personnel are described in FDA/OHR

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Position Management Handbook for Supervisors.

- E. Personnel are authorized to perform specific laboratory activities according to section 6.2.6 and local documents.
- F. Personnel competency is monitored through onsite reviews, reporting and worksheet write-ups, demonstration through documentation of the required instrument maintenance and function checks, results obtained on proficiency test samples, number of samples analyzed satisfactorily and QC samples within established criteria.

6.2.6. Personnel Authorization

The Laboratory Management authorizes personnel to perform specific laboratory activities, including but not limited to:

- A. Development, modification, verification and validation of methods;
- B. Analysis of results, including statements of conformity or opinions and interpretations;
- C. Report, review and authorization of results;

Records of authorizations, demonstration of competence, education, training, and experience are maintained by the laboratory and dated. Training files are maintained and include these records.

Related Procedures/References

- ORA Laboratory Manual, Volume II, ORA-LAB.5.2 Personnel Training and Competency Management

6.3. Facilities and Environmental Conditions

6.3.1. Suitability of Facilities and Environmental Conditions

The laboratory environmental conditions facilitate the correct performance of analytical testing. Examples of environmental influences are energy sources, lighting, biological sterility, dust, humidity, and temperature. The laboratory monitors critical environmental conditions to ensure that results and the quality of the measurement are not adversely affected or invalidated.

6.3.2. Documentation of Requirements for Facilities and Environmental Conditions

Test methods and environmental monitoring procedures used by the laboratory include instructions addressing applicable environmental conditions.

6.3.3. Monitoring, Controlling and Recording Environmental Conditions

Environmental conditions requiring monitoring include, but are not limited to:

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- A. room temperature and humidity,
- B. air flow rates for chemical fume hoods,
- C. biosafety hoods and laminar flow hoods,
- D. metal contamination on benches and hoods in laboratories performing metal analysis,
- E. microbiological contamination on bench surfaces and hoods in microbiology
- F. laboratories, and
- G. air sampling for microbiological contamination in microbiology areas.

Where environmental controls are needed, the environmental conditions are recorded.

Testing activities are stopped when the environmental conditions invalidate the test results or adversely affect quality control. Monitoring activities are conducted as part of the laboratory test or calibration methods.

6.3.4. Measures to Control Facilities

The following measures to control facilities are implemented, monitored and periodically reviewed:

A. Access and use of areas affecting laboratory activities

ORS laboratories are limited access areas. Access and use is controlled by, but is not limited to:

- 1. issuance of keycards for entrance,
- 2. escorting visitors,
- 3. issuance of identification badges, and
- 4. the use of security guards.

B. Housekeeping

Laboratory areas are maintained clean and orderly to prevent contamination of samples and to facilitate the efficiency of laboratory operations. Volume II, Section 2, ORA-LAB.5.3 Facilities and Environmental Conditions specifies minimum housekeeping measures. The laboratory's Chemical Hygiene Plan and Hazardous Waste Management Plan include measures taken to ensure good housekeeping in the laboratory.

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C. Cross-contamination

Separate areas are maintained for incompatible activities. Measures taken to prevent cross-contamination include, but are not limited to:

1. chemistry laboratories are separated from microbiology laboratories,
2. sample receiving, and storage are conducted in designated areas,
3. separate storage for standards and reference materials and cultures, and
4. microbiology media preparation and sterilization are separated from work areas.

Related Procedures/References

- ORA Laboratory Manual, Volume II, ORA.LAB.5.3, Facilities and Environmental Conditions.
- Laboratory Chemical Hygiene Plan.
- Laboratory Waste Management Plan.

6.3.5. **Work Performed Outside the Laboratory's Permanent Control**

In the event staff perform laboratory activities at sites outside of the laboratory's control, facility and environmental requirements are met.

6.4. **Equipment**

6.4.1. **Access to Laboratory Equipment**

The laboratory has sample preparation, measurement and test equipment for the correct performance of the tests and calibrations. The laboratory also has ancillary equipment for processing samples and for processing data. Also see section 6.5 Metrological Traceability.

The laboratory or other ORA component, i.e., Office of Regulatory Science, purchases the equipment used by the laboratory. Maintenance contracts are established as needed. In those cases where the laboratory leases equipment it has direct control concerning its use. Leased equipment is managed in the same manner as purchased equipment according to the management system requirements.

ORS laboratories maintain an equipment inventory of all laboratory equipment used to perform regulatory testing.

6.4.2. **Equipment Outside the Laboratory's Permanent Control**

If for any reason equipment leaves the direct control of the laboratory the

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laboratory ensures the equipment requirements are met before using the equipment.

6.4.3. Procedure for Handling, Transport, Storage, Use and Planned Maintenance of Equipment

The laboratory has procedures in Volume II, Section 2, ORA-LAB.5.5 Equipment and ORA-LAB.5.6 Measurement Traceability for the safe handling, transport, storage, use and planned maintenance of equipment to ensure proper functioning and to prevent contamination or deterioration.

6.4.4. Verification of Equipment Prior to Being Placed or Returned into Service

The equipment performance is verified, and verification records are maintained. Equipment is to meet the laboratory's testing parameters and conform to standard specifications before being placed or returned into service.

Procedures for equipment verification are provided in Volume II, Section 2, ORA-LAB.5.5 Equipment.

6.4.5. Equipment Accuracy/Uncertainty

Equipment and its software used for testing are to achieve the accuracy expected, measurement uncertainty required, and comply with specifications of the testing concerned.

The uncertainty contributions are addressed in ORA Laboratory Manual, Volume II, Section 2, ORA-LAB.5.4.6. Estimation of Uncertainty of Measurement.

6.4.6. Equipment Calibration

Measuring equipment is calibrated when the measurement accuracy or uncertainty affect the reported results and/or calibration of the equipment is required to establish metrological traceability of the reported result.

Procedures for equipment calibration are provided in Volume II, Section 2, ORA-LAB.5.5 Equipment and ORA-LAB.5.6 Measurement Traceability.

6.4.7. Calibration Program

The equipment calibration program is defined in Volume II, Section 2, ORA-LAB.5.5 Equipment and ORA-LAB.5.6 Measurement Traceability. These procedures are reviewed and revised according to ORA-LAB.4.3 Document Control and Management.

6.4.8. Calibration Status

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Equipment under the control of the laboratory and requiring calibration, or having a defined period of validity, is labeled or coded to indicate the calibration status or period of validity. Alternatively, equipment calibration status may be identified in an associated record to indicate the status of calibration.

6.4.9. Out of Service

Equipment that has been subjected to overloading or mishandling, gives suspect results, or has been shown to be defective or outside specified limits, is taken out of service. It is isolated to prevent its use or clearly labeled or marked as being “Out of Service” to prevent its use until it has been repaired and shown by calibration or test to perform correctly.

Laboratory personnel examine the effect of the defect or departure from specified limits on previous tests according to Volume I, Section 7.10 Non-conforming Work.

6.4.10. Calibration Confirmation

Intermediate calibration confirmation checks are performed to maintain confidence in the calibration status of the equipment. These checks are conducted according to the procedure in Volume I, Section 7.7 Ensuring the Quality of Test Results.

Metrological confirmation for reference standards and reference materials included in the calibration program is conducted according to a schedule addressed in the procedure in Volume II, Section 2, ORA-LAB.5.5 Equipment. The confirmation is conducted to maintain confidence in the calibration status of reference standards and reference materials.

6.4.11. Correction Factors

Where calibrations give rise to a set of correction factors, these factors are updated and implemented to meet specified requirements.

6.4.12. Safeguards

Test and calibration equipment, including both hardware and software, are safeguarded from adjustments that would invalidate the test or calibration results. Safeguards are provided using access control to the laboratory.

6.4.13. Equipment Records

Records are maintained of each item of equipment and its software that can influence laboratory activities according to the procedure in Volume II, Section 2, ORA-LAB.5.5.1 Instrument and Equipment Documentation and Records.

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The records include at least the following items, where applicable:

- A. identity of equipment, including its software and firmware version;
- B. manufacturer's name, type identification, and serial number or other unique identification;
- C. evidence of verification that equipment conforms with specified requirements;
- D. current location of the equipment;
- E. calibration dates, results and copies of reports and certificates of calibrations, adjustments, acceptance criteria, and the due date of next calibration or the calibration interval;
- F. documentation of references materials, results, acceptance criteria, relevant dates and the period of validity;
- G. maintenance plan and maintenance carried out to date, where relevant to the performance of the equipment; and
- H. details of any damage, malfunction, modification or repair to the equipment.

6.5. Metrological Traceability

6.5.1. Establishing and maintaining metrological traceability

The program for calibration of equipment demands that calibrations and measurements made by the laboratory are traceable to the International System of Units.

Calibration laboratories providing services to ORS laboratories are to provide evidence of measurement traceability of its own measurement standards and measuring instrument to the SI. This is done by means of an unbroken chain of calibration or comparisons linking them to primary standards of the SI units of measurement. Such primary standards are those used by national measurement standards.

Calibration certificates issued by calibration laboratories are to include the measurement results, including the measurement uncertainty and a statement of conformance with an identified metrological specification.

6.5.2. Ensuring measurement results are traceable

- A. Calibration laboratories providing services to ORS laboratories are to provide documentation demonstrating measurement capability and competence to perform the calibration services requested by ORS laboratories.

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B. A reference material is a homogenous and well characterized substance used for standardization of equipment used in the testing process. Reference materials are traceable to national or international standard reference materials (SRMs), such as National Institute of Standards and Technology (NIST), or certified reference materials (CRMs) from competent suppliers of reference materials.

The measurement integrity of internal reference materials generated by the laboratory is evaluated against either standard reference materials or certified reference materials from an independent source when it is technically and economically possible.

C. The measurement traceability to SI units may be achieved by measurements related to national measurement standards. National measurement standards may be used as primary standards that are primary realizations of the SI units or agreed representations of SI units. National measurement standards based on fundamental physical constants, or standards calibrated by another national metrological institute may be use as primary standards.

6.5.3. **Non-traceability of reference standards to SI units**

Calibrations that cannot provide strict measurement traceability to SI units are conducted such that the calibration results can provide confidence in the measurements made in the course of the analyses. Traceability alternatives to SI units are described in the procedure in Volume II, Section 2, ORA-LAB.5.6 Measurement Traceability.

6.6. **Externally Provided Products and Services**

6.6.1. **Suitability of Externally Provided Products and Services**

The laboratory ensures that only suitable externally provided products and services that affect laboratory activities are used when they are intended for incorporation into the laboratory's activities and/or used to support the operation of the laboratory.

ORS laboratories do not subcontract routine analyses within their scope of accreditation.

Collaborative activities conducted with external laboratories, such as universities, are research in nature and do not involve the routine analysis of FDA samples.

Subcontracting Laboratories

Based on workload fluctuations and resource needs, ORS laboratories may request samples assigned to other FDA laboratories for analysis. Samples are

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administratively transferred after arrangements are made to ensure that the receiving laboratory has the capacity and capability to complete it in a timely manner.

Samples are shipped per Department of Transportation (DOT), United States Post Office (USPS), and carrier regulations. ORA Laboratory Manual (LM), Volume III, Section 2, Chain of Custody describes the procedure for documenting administratively transferred samples (ATS).

Notification of Customer

FACTS (Field Accomplishment and Compliance Tracking System), which is accessible to the customer, serves as a notice of the transfer.

Laboratory Responsibility

The FDA laboratory to which the sample has been transferred assumes responsibility to the collector for the work.

Related Procedures/References

- ORA Laboratory Manual, Volume III, Section 2, Chain of Custody – Sample Handling

6.6.2. Purchasing services and supplies

- A. ORA-LAB.4.6 Purchasing and Receipt provides policies and instructions for procurement of supplies, materials, equipment, and services that affect the quality of tests. It documents the procedures for purchase, reception, and storage of supplies, materials, and equipment relevant to tests.
- B. The laboratory or designated purchasing agents use Federal Acquisition Regulations (FAR) and related procedures for the procurement of materials, supplies and services that critically affect the quality of the tests or calibrations. These procedures describe the process for the selection, purchase, reception and storage of equipment, services and supplies, including reagents and laboratory consumable materials, used in the performance of the tests and calibrations. Each laboratory has work instructions describing the processing of requisitions.
- C. Purchasing documents for items affecting the quality of laboratory output describe the services or supplies ordered. These purchasing documents are reviewed and approved for technical content prior to submission.

Records of supplier evaluations are maintained by purchasers of laboratories equipment, services, and supplies.

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The laboratory's purchasing procedure describes how purchased equipment, supplies, services, reagents, and consumable materials that critically affect the quality of tests or calibrations are inspected or verified prior to use. Inspection or verification criteria are used to establish conformance with requests made by the customer, included in standard specifications, or defined in the methods.

- D. Records of unsatisfactory materials and supplies and their disposition are maintained. These records establish trends in vendor performance and ensure that continuing quality material is accepted. A vendor is considered unacceptable and is not used when the quality of product or service does not meet expectations or specifications.

6.6.3. **Communicating requirements to external providers**

Critical specifications and requirements are clearly described on the purchasing requests and are communicated to external providers by the Purchasing Agent. These criteria include:

- A. The products and services to be provided;
- B. The acceptance criteria; and
- C. Competence, including any required qualification of personnel

ORS laboratories do not subcontract routine analyses within their scope of accreditation.

Related Procedures/References

- Government Accounting Office (GAO) Policy and Procedures Manual
- SMG 2610 Procurement and Supply Management
- Federal Acquisition Requirements
- Office of Management and Budget (OMB), General Service Administration (GSA), HHS, Federal Property Management Regulations (FPMR), FDA and ORA manuals, specific issuances
- Public Law (PL) 95-507

7. Process Requirements

7.1. Review of Requests, Tenders, and Contracts

7.1.1. Procedure

ORA, Division of Planning and Evaluation (DPE) develops and issues the Annual Fiscal Year (FY) Workplan for ORA field units. The portion of the workplan concerned with the ORS laboratories is a cooperative effort among

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the Centers, ORA Field Committee, and ORS. The workplan is based on several factors such as the budget, the number of analysts and amount of resources, the Commissioner’s performance goals, the compliance program accomplishment goals, the inventory of regulated industry maintained by the field units, and FDA-targeted products. Distribution of assignments is by Program Assignment Code (PAC) and full time equivalent (FTE) hours within the different program areas. The compliance programs specify or cite the methods for analyses. The ORS laboratories and ORS review the annual workplan to ensure that each laboratory has the capability and resources to provide the requested services. Any differences between the workplan and the laboratory capability are resolved in accordance with GUIDE-000250 A Guide to Understanding the Program-based Forecast for Work planning or through consultation with ORS management.

In addition to the workplan, assignments may be issued to ORS laboratories by an ORA headquarters unit or a Center. Multiple program assignments and high priority requests for work are approved per FDA Field Management Directive 17, ORA Field Assignments-Guidelines for Issuance by Headquarters. Such assignments are cleared through the Office of Strategic Planning and Operational Policy (OSPOP). Assignments specify or cite the methods for analyses.

Requests not covered by compliance programs or assignments are reviewed prior to receipt of samples by the laboratory’s management when possible.

The results of this process are discussed and documented as part of the laboratory’s annual management review.

Subcontracting Laboratories

The policies regarding the use of subcontracting laboratories are found in Volume I Subsection 6.6 Externally Provided Products and Services. The customer requesting collaborative testing by laboratories outside of ORA is responsible for the work done by such labs. ORA is not responsible for such work under these circumstances.

Based on workload fluctuations and resource needs, ORS laboratories may request samples assigned to other FDA laboratories for analysis. Samples are administratively transferred after arrangements are made to ensure that the receiving laboratory has the capacity and capability to complete it in a timely manner.

FACTS, which is accessible to the customer, serves as a notice of the transfer.

Laboratory methods are selected based on compliance programs. When the customer does not specify the method to be used, a standard method is preferred for use. If a standard method is not found, the laboratory may use

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either a non-standard method or modify a method for use with the concurrence of the customer. The non-standard or modified method is validated according to Volume I, subsection 7.2.2 Validation of Methods.

7.1.2. Method Requested is Inappropriate or Out of Date

The laboratory informs the customer when the method proposed by the customer is considered to be the incorrect choice or the incorrect revision for the intended purpose. This is done as part of contract review addressed in section 7.1.1.

7.1.3. Statements of Conformity

When the customer requests a statement of conformity to a specification or standard for the test, the specification or standard and the decision rule are clearly defined in the compliance programs or standard. Otherwise, the laboratory communicates the decision rule selected to the customer and obtains their agreement. See section 7.8.6 Reporting Statements of Conformity

7.1.4. Differences and Deviations

The ORS laboratories and ORS review the annual workplan to ensure that each laboratory has the capability and resources to provide the requested services. Any differences between the workplan and the laboratory capability are resolved prior to commencing work and in accordance with GUIDE-000250 A Guide to Understanding the Program-based Forecast for Work planning, or through consultation with ORS management.

7.1.5. Communicating with the customer

Requests for deviations from work assignments or compliance programs are processed by the Office of Regulatory Science (ORS). ORS interacts with the customer to determine whether the requested changes are acceptable and do not impact the integrity of the laboratory or the validity of the results. Records of contract changes are maintained.

7.1.6. Amendments to Contracts

If a contract needs to be amended after work has commenced, the same contract review process is repeated, and any amendments are communicated to all affected personnel named in the contract.

7.1.7. Customer Service

The laboratory affords the requesting customer cooperation to clarify the customer's request within the framework of the contract review process

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described in Volume I, Section 7.1.1. The laboratory maintains communications regarding deviations from contract work. Communications regarding compliance programs, workplan and assignments are conducted through ORS.

The opportunity for the customer to witness laboratory activity is given upon request, providing the laboratory can maintain confidentiality to other customers during such cases.

7.1.8. Records of Review

ORS laboratories maintain records of workplan reviews, changes, and change requests. Records are also maintained of discussions regarding ad hoc assignments.

Related Procedures/References

- GUIDE-000250 A Guide to Understanding the Program-based Forecast for Work planning
- FDA Field Management Directive 17, ORA Field Assignments-Guidelines for Issuance by Headquarters
- Annual Workplan

7.2. Selection, Verification and Validation of Methods

7.2.1. Selection and Verification of Methods

Specific requirements for the Verification and Validation of methods process for ORS laboratories are outlined in ORA-LAB.5.4.5 Method Validation and Verification.

7.2.1.1. The scope of test technologies and associated method source routinely used are identified in the laboratory's accreditation program documentation.

The estimation of the uncertainty of measurement is addressed in Volume I, subsection 7.6. Volume I, Section 7.7 Ensuring the Validity of Results of this manual describes the quality control processes, including the application of statistical techniques, for supporting test and calibration data.

7.2.1.2. Laboratory methods and supporting documents are controlled according to Volume I, Section 8.3 Control of Management System Documents and are readily available.

7.2.1.3. Laboratory methods are selected to meet the customer's need as addressed in Volume I, Section 7.1 Review of Requests, Tenders

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and Contracts. The laboratory ensures that it uses the latest valid version of analytical methods unless not appropriate or possible to do so.

Standard methods are those 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. Standard methods are preferred for use and are verified for use in the laboratory. A standard method may be supplemented with additional details in the form of a laboratory procedure to ensure consistent application. Those methods specified by the manufacturer of the equipment are considered as standard methods. Standard methods are verified according to the procedure, Volume II, Section 2, ORA-LAB.5.4.5 Methods, Method Verification and Validation.

- 7.2.1.4. When the customer does not specify the method to be used, a standard method is preferred for use. If a standard method is not found, the laboratory may use either a non-standard method or modify a method for use with the concurrence of the customer. The non-standard or modified method is validated according to Volume I, subsection 7.2.2 Validation of Methods.

The laboratory informs the customer when the method proposed by the customer is considered to be the incorrect choice or the incorrect revision for the intended purpose. This is done as part of contract review addressed in Volume I, Section 7.1 Review of Requests, Tenders and Contracts.

- 7.2.1.5. Standard methods are verified according to the procedure, Volume II, Section 2, ORA-LAB.5.4.5 Methods, Method Verification and

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Validation.

Records of the verification are retained by the ORS laboratories. If the method is revised by the issuing body, verifications are repeated to the extent necessary.

- 7.2.1.6. Non-standard methods are those methods not taken from authoritative, validated sources. A nonstandard method has not undergone validation, such as a collaborative study or process to evaluate the method's performance capabilities.

Non-standard methods are selected for use when a customer request cannot be addressed with the use of a standard method. Such methods are subject to agreement with the customer and a clear specification of the customer's work requests, including the purpose of the test, is made. This process is described for contract amendments in Volume I, subsection 7.1 Amendments to Contracts with laboratory management concurrence. Non-standard methods are validated according to Volume I, subsection 7.2.2 Validation of Methods.

When a laboratory develops methods for its own use refer to Volume II, Section 2, ORA-LAB.5.4.5. This procedure provides the planned activities, identification of competent personnel, and resources. Method development plans are reviewed periodically to confirm the customer's requirements are still being met. Any modifications to the development plan shall be approved and authorized. Laboratory developed methods adopted by the laboratory are used if they are validated according to Volume I, subsection 7.2.2 Validation of Methods.

- 7.2.1.7. Deviations from test methods are documented, technically justified, authorized, and where circumstances call for it, accepted by the customer according to Volume II, Section 2, ORA-LAB.5.10 Reporting Laboratory Data.

7.2.2. Validation of Methods

- 7.2.2.1. The laboratory validates non-standard methods, laboratory developed methods, and modified standard methods including use outside the intended scope or otherwise modified. Validation is conducted to confirm that the methods are fit for the intended use, relevant to the customers' needs, and consistent with specified requirements. The validation is as extensive as is necessary to meet the needs of the given application or field of application.

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7.2.2.2. When changes are made to a validated method, the influence of such changes shall be determined and where they are found to affect the original validation, a new method validation shall be performed.

7.2.2.3. The validation process addresses the needs of the given application or field of application. The laboratory analyst records the results obtained according to the procedure, Volume II, Section 2, ORA-LAB.5.4.5 Methods, Method Verification and Validation. The validation results include a statement as to whether the method is fit for the intended use. The needs of the customer define the intended use of the method. The attributes and data quality objectives include but are not limited to:

- accuracy,
- precision,
- specificity,
- detection limit,
- limit of quantitation,
- linearity,
- range, and
- ruggedness or robustness.

If all the data quality objectives are met as indicated by the data collected, the method is considered as validated.

7.2.2.4. The following records are maintained for each validation:

- the validation procedure used;
- specification of the requirements
- determination of the performance characteristics of the method;
- results obtained;
- a statement on the validity of the method, detailing its fitness for the intended use.

7.3. Sampling

ORS laboratories do not routinely perform sampling in the sense of collecting a representative sample from a product lot to represent the whole.

Sample Collection Conducted by the Customer: Most test samples are

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obtained and sent to the laboratory by ORA inspectional staff. Instructions for sample collection, including methods and sampling plans, by such personnel are provided in the Investigations Operations Manual (IOM) Chapter 4.

Occasionally, laboratory personnel are consulted about sampling parameters such as sample type or size or guidance for a sampling or analytical need. The ORS laboratories, however, exert no direct control over such sampling and do not have responsibility for sampling.

Sampling data (i.e. date and time of sampling, description, environmental conditions, collector identification, etc.) required as part of testing is included in the Collection Report accompanying the request in FACTS. When the request is entered, a unique identifier is assigned to the sample.

Sampling conducted by ORS laboratories involves for the most part those analyses that call for a portion or aliquot of the total sample received by the laboratory to be analyzed. Generally, this calls for mixing or preparing of samples to assure homogeneity before portions are taken for analysis. Sample preparation and subsampling protocols are found in the analytical methods, compliance programs, and assignments.

7.4. Handling of Test or Calibration Items

The laboratory procedure in Volume II, Section 2, ORA-LAB.5.8 Sample Management, describes the receipt, processing, protection, storage, retention and disposal of samples. This procedure also provides the details for handling and protecting test items from deterioration, loss or damage during storage and processing. The laboratory has arrangements for storage and security that protect the condition and integrity of samples. Sample security arrangements apply both in the laboratory and in the custodial areas.

- 7.4.1. The laboratory has a system for uniquely identifying samples. The sample number is used to track its progress from the time the sample is collected in the field until the analysis is completed and the sample is disposed. The sample number is also used to provide traceability between the sample and the data. The numbering system also provides traceability during transfer of samples within the laboratory and between ORS laboratories in the case of administratively transferred samples. The identification system is described in Volume II, Section 2, ORA-LAB.5.8 Sample Management.
- 7.4.2. When samples received do not meet established acceptance criteria, for example, contract/program specifications, analysis requested, abnormalities or departures from normal or specified conditions, and chain of custody criteria, these deviations are recorded according to Volume II, Section 2, ORA-LAB.5.8 Sample Management. The customer is consulted prior to commencement of analysis for further instructions. Communication

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with the customer is recorded in accordance with ORA-QMS.014 Sample Feedback Report Process.

Sample abnormalities or departures are also noted on the analytical worksheet.

- 7.4.3. When samples and calibration items have specific environmental conditions, those conditions are maintained, monitored and recorded. Monitoring records are collected according to established procedures. These activities are conducted according to the policies stated in Section 6.3 Facilities and Environmental Conditions.

7.5. Technical Records

- 7.5.1. Technical records for all activities that contribute to data reporting, depending on the type of analysis, include the original observations, derived data, calculations, standard preparation, instrument printouts, and results. These records contain the date each activity is completed and the identity of all persons who perform each activity throughout the process, including those who review the data and results.

Observations, data, and calculations are recorded at the time they are made and are identifiable to the activity performed.

The records of each test contain sufficient information to repeat the test under conditions as close as possible to the original. This information includes environmental conditions that affect the test and factors that affect the measurement results and its associated measurement uncertainty.

Staff records, equipment calibration, and verification reports are retained in accordance with the laboratory's control of records procedure. These records contain sufficient information to establish an audit trail. The requirements for an audit trail in laboratory records are outlined in ORA-LAB.4.13 Record and Data Management.

Data is reported electronically in FACTS and/or scanned and uploaded into Compliance Management Services (CMS), both ORA web-based programs.

The collection report in FACTS identifies the personnel responsible for sampling. The FDA form FD-431a includes the identity of the personnel responsible for performance of each test and for checking the results.

- 7.5.2. ORS laboratories ensure changes to technical records can be tracked to the previous version or to original observations. Both the original and amended data and files are retained, including the date the record was changed, an indication of what was changed and the person responsible

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for the alteration.

7.6. Evaluation of Measurement Uncertainty

7.6.1. Uncertainty Components

When estimating the uncertainty of measurement, all important uncertainty components are recorded in the uncertainty records for each determination and test technology as addressed in the procedure Volume II, Section 2, ORA-LAB.5.4.6, Estimation of Uncertainty of Measurement.

7.6.2. Procedure for Calibration Activities

ORS laboratories do not perform calibration activities. At such time that calibration activities are performed, the ORS laboratories are to address the requirements of ISO/IEC 17025:2017.

7.6.3. Procedure for Testing Activities

The laboratory has a procedure, Volume II, Section 2, ORA-LAB.5.4.6, Estimation of Uncertainty of Measurement, to estimate the uncertainty of measurement for testing activities.

The application of details in cases where the nature of the test method may preclude rigorous, metrologically and statistically valid, calculation of uncertainty of measurement is addressed in the procedure.

An attempt is made to identify all the components of uncertainty and make a reasonable estimation of the measurement uncertainty. This estimation is based on knowledge, experience, and validation data of the performance of the method and on the measurement scope. If needed as a part of the laboratory data, the uncertainty estimation is reported according to the procedure, Volume II, Section 2, ORA-LAB.5.4.6 Estimation of Uncertainty of Measurement.

7.7. Ensuring the Validity of Results

7.7.1. Quality Control Procedures

The laboratory has quality control procedures to validate the results of tests undertaken according to Volume II, Section 2, ORA-LAB.5.9 Assuring the Quality of Test Results.

The monitoring data is recorded in such a way that trends may be detected, for example, statistical process control charts. Monitoring activities are planned and evaluated according to Volume II, Section 2, ORA-LAB.5.9 Assuring the Quality of Test Results. Monitoring techniques may include, but are not limited to, the following:

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- A. Scheduled use of certified reference materials or quality control materials;
 - B. Use of alternative instrumentation that has been calibrated to provide traceable results;
 - C. Functional check(s) of measuring and testing equipment;
 - D. Use of check or working standards with control charts;
 - E. Intermediate checks on measuring equipment;
 - F. Replicate tests using the same or different methods;
 - G. Retesting of reference materials and retained customer samples;
 - H. Correlation of results from tests conducted for different characteristics of a sample;
 - I. Review of reported results;
 - J. Scheduled participation in interlaboratory comparison or proficiency-testing and calibration programs as described in ORS.002, National Check Sample Program;
 - K. Testing of blind samples.
- 7.7.2. ORS laboratories participate in proficiency testing programs and/or interlaboratory comparisons other than proficiency testing, where available and appropriate.
- 7.7.3. The laboratory has defined the criteria for quality control data and performs analysis by such means as control charting. When data is found to be outside the established criteria, action is taken in accordance with ORA-LAB.4.9 Control of Nonconforming Work.

7.8. Reporting Results

7.8.1. General Requirements

Test reporting is addressed in the ORA Laboratory Manual procedure found in Volume II, Section 2, ORA-LAB.5.10 Reporting Laboratory Data. This procedure gives the details for reporting data using consistent reporting formats for laboratory worksheets. Results are reported on analytical worksheets and in FACTS and/or LIMS.

- 7.8.1.1. Laboratory results are reviewed and authorized for release by supervisors or designees. Reports are reviewed for accuracy, clarity and objectivity. Laboratory management expresses its opinion and interpretation of the compliance or non-compliance of the results

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through the laboratory classification assigned to each sample. This laboratory classification is recorded in FACTS and/or LIMS and may be recorded on the FDA form FD-465 as well. The laboratory classifications are defined in the ORA Laboratory Manual Vol. III, Section 3.

- 7.8.1.2. Laboratory reports, depending on the type of analysis, include the original observations, derived data, calculations, standard preparation, instrument printouts, and results. These reports are retained until closed in FACTS and/or LIMS and final review is performed. An electronic test report is in FACTS and/or LIMS. Staff records, equipment calibration, and verification reports are retained in accordance with the laboratory's control of records procedure.

The records contain sufficient information to establish an audit trail.

The records of each test contain sufficient information in order to repeat the test under conditions as close as possible to the original. This information includes factors that affect uncertainty and any environmental conditions that affect the test.

The collection report in FACTS identifies the personnel responsible for sampling. The FDA form FD-431a includes the identity of the personnel responsible for performance of each test and for checking the results.

- 7.8.1.3. Test reporting is addressed in the procedure found in Volume II, Section 2, ORA-LAB.5.10 Reporting Laboratory Data. This procedure gives the details for reporting data using consistent reporting formats for laboratory worksheets.

7.8.2. **Common Requirements for Reports (test, calibration or sampling)**

7.8.2.1. **Format**

The format for laboratory worksheets is designed to accommodate the type of test conducted to minimize the possibility of misunderstanding or misuse. The worksheet format is described in Volume II, Section 2, ORA-LAB.5.10 Reporting Laboratory Data.

Subcontracting laboratories are not utilized by ORS laboratories, therefore, there is no such data found for incorporation in the analysis report to the customer.

7.8.2.2. **Data Provided by Customer**

Analysts describe the sample as received, including any information provided

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by the customer, on the sample worksheet in the description of sample block (Block 7). When information supplied by the customer can affect the validity of the results, a disclaimer statement is included on the worksheet.

7.8.3. Specific Requirements for Test Reports

7.8.3.1. Test Report Requirements

The following information is included in test reports for the interpretation of the test results:

- A. Information on test conditions, such as environmental conditions;
- B. Where relevant, a statement of conformance or non-conformance with specifications;
- C. The measurement uncertainty presented in the same unit as the measurand, or in a term relative to the measurand when:
- D. It is relevant to the validity of the test results;
- E. A customer requires it, or;
- F. The measurement uncertainty affects conformity to a specification limit;
- G. Opinions and interpretations as detailed in Volume I, Section 7.8.7; and,
- H. Additional information that may be requested by methods, customers or groups of customers.

7.8.3.2. ORS laboratories do not routinely conduct sampling in the sense of collecting a representative sample from a product lot to represent the whole.

7.8.4. Specific Requirements for Calibration Certificates

ORS laboratories conduct in-house calibration activities on measuring and test equipment only and, therefore, do not issue calibration certificates. In-house calibrations are documented by a report, or sticker, or other suitable method.

7.8.5. Reporting Sampling – specific requirements

In addition to the instructions listed in Sections 7.8.1 General Requirements and 7.8.3. Specific Requirements, sampling information and conditions are posted to the laboratory for review on the FACTS sample collection record.

7.8.6. Reporting Statements of Conformity

7.8.6.1. Decision Rules

Statements of conformity to a specification or standard require the use of a

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decision rule to take into account the uncertainty associated with method. Most decision rules used by ORS laboratories are documented in the compliance programs or standard methods. When the decision rule is not provided, the laboratory must document the decision rule and account for the level of risk associated with the decision rule used.

7.8.6.2. **Reporting Statements of Conformity**

Statements of conformity reported on worksheets clearly identify:

- A. The results the statement applies to;
- B. Which specifications or standards were met, or not met;
- C. The decision rule applied (unless it is defined in the specification or standard).

7.8.7. **Reporting Opinions and Interpretations**

Laboratory management expresses its opinion and interpretation of the compliance or non-compliance of the results through the laboratory classification assigned to each sample. This laboratory classification is recorded in FACTS and/or LIMS and may be recorded on the FDA form FD-465 as well. The laboratory classifications are defined in the FDA Data Codes Manual.

Records are maintained of conversations expressing opinions and interpretations about a sample with the customer.

7.8.8. **Amendments to Reports**

Material amendments to analytical findings after issue are made only in the form of an additional document. They are flagged “Additional Analyses” in accordance with procedure ORA-LAB.5.10 Reporting Laboratory Data of Volume II. Amendments are to meet the same reporting criteria. Any changed information is clearly identified and where appropriate, the reason for the change is included in the report.

Related Procedures/References

- ORA Lab Manual, Volume II, ORA-LAB.5.10 Reporting Laboratory Results.
- FDA Regulatory Procedures Manual.

7.9. **Complaints**

7.9.1. The ORS laboratories have a complaint process describing the handling of complaints received from any party. See ORA-LAB.4.8 Complaints and Feedback. In addition to the resolution of these complaints, improvement

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in the area of concern is addressed and implemented in most cases.

- 7.9.2. The process for handling complaints is documented in ORA-LAB.4.8 and is available to any interested party on the FDA internet site. The laboratory confirms whether the complaint relates to laboratory activities that it is responsible for and, if so, then addresses it.
- 7.9.3. The process for handling complaints includes the following:
 - A. Description of the process for receiving, validating, investigating the complaint, and deciding appropriate actions to respond to it;
 - B. Tracking and recording complaints, including actions taken to resolve them;
 - C. Ensuring appropriate action is taken.
- 7.9.4. The laboratory receiving the complaint will gather all information required to investigate, validate, address, and review the complaint and its outcome.
- 7.9.5. When possible, the laboratory will acknowledge receipt of the complaint, provide progress reports with the outcome of resolution, and formal notice of completion to the complainant.
- 7.9.6. Communications to the complainant is addressed in ORA-LAB.4.8.

7.10. Nonconforming Work

- 7.10.1. The ORS laboratories have a control of non-conforming work procedure that is implemented when any aspect of their activities, or the results of this work, does not conform to requirements of the management system, testing methods, or the requests of the customer. This procedure addresses the following elements:
 - A. responsibilities and authorities for the management of identified non-conforming work to include taking actions such as the halting of work and/or the withholding of test reports based upon risk levels established by the laboratory
 - B. actions are based upon the risk levels established by the laboratory;
 - C. an evaluation of the significance of non-conforming work including an impact analysis on previous results and, if necessary, recall of work with notification to the customer
 - D. remedial action taken, together with any decision about the acceptability of the non-conforming work

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1. The customer is notified if investigations show that non-conformances have affected work performed for or data reported to the customer. This notification is documented.

E. responsibility for authorizing the resumption of work.

7.10.2. Records of nonconforming work and actions taken are maintained in QMiS.

7.10.3. If the non-conforming work could recur, or there are other significant problems identified, the corrective action procedures in Volume I, Section 8.7 Corrective Action are promptly followed.

Related Procedures/References

- ORA Laboratory Manual, Volume II, ORA-LAB.4.9 Control of Nonconforming Work

7.11. Control of Data and Information Management

ORS laboratories have access to the data and information needed to perform laboratory activities through various electronic records management systems including FACTS, LIMS, QMiS, and paper records maintained according to ORA-LAB.4.13 Record and Data Management.

7.11.1. ORA information management system applications used for the acquisition, processing, recording, reporting, storage or retrieval of data are validated prior to introduction by the FDA's Office of Information Systems Management.

If computer software is developed by the user, its development is authorized, documented in detail and algorithms are validated prior to implementation.

Changes to laboratory software configuration or modifications to commercial off-the-shelf software are also authorized, documented and validated prior to use.

7.11.2. ORS laboratories have processes for the protection of data to include, but not limited to data integrity, data confidentiality during entry, collection, storage, transmission and processing. The processes also ensure safeguards are in place to prevent unauthorized access to or amendment of records.

Information management system failures are recorded and appropriate immediate and corrective actions are taken.

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- 7.11.3. Laboratory information systems managed and maintained off-site meet all applicable requirements of ISO 17025:2017.
- 7.11.4. Instructions, manuals and reference data relevant to the laboratory information systems are readily available to personnel through the document control process (see section 8.3).
- 7.11.5. Calculations and data transfers are reviewed before the data is reported. All changes are identified and verified where they occur. This process is detailed in the procedure for laboratory quality control identified in Volume I, Section 7.7 Ensuring the Validity of Results.

8. Management System Requirements

8.1. Options

8.1.1. General

ORS laboratories have established, documented, implemented, and maintained a management system capable of supporting and demonstrating the consistent achievement of the requirements of ISO/IEC 17025:2017 to assure the quality of laboratory results. In addition to meeting the requirements outlined in sections 4 to 7 of this document the Standard requires ORS laboratories implement a management system in accordance one of the two following options.

8.1.2. Option A

ORS laboratories follow the requirements for option A, outlined in the following sections 8.2 to 8.9.

8.1.3. Option B

Option B of ISO/IEC 17025:2017 addresses minimal requirements for laboratories with a separate management system either certified to or at least structured to the requirements of ISO 9001. ORS laboratories do not fall within this category.

8.2. Management System Documentation (Option A)

8.2.1. Management System Policy

Mission

ORA's mission statement states "ORA protects consumers and enhances

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public health by maximizing compliance of FDA regulated products and minimizing risk associated with those products”. ORS laboratories are committed to providing testing that meets both the needs of the customers and the requirements of ISO/IEC 17025:2017 and to continually improve the effectiveness of the management system. Testing results are reported within stated limits of accuracy, precision, and detection limits as described in the methods used for analysis.

Commitments to Quality Issued by Director, Office of Regulatory Science

A. Good Professional Practice and the Quality of Testing

ORS laboratories are committed to the Standards of Ethical Conduct which define the obligations of public service issued under Executive Order 12674. Testing is conducted per the policies stated in Volume I, subsections 3 and this section. The laboratory management and personnel are committed to performing quality activities to assure integrity, accuracy, precision, reliability and timeliness of the data.

B. Standard of Service

The laboratory’s standard of service for the testing program is defined by the ISO/IEC 17025:2017 requirements, FDA regulatory needs included as part of the laboratory methods, and the following:

1. Established and maintained documented procedures for laboratory operation based upon consensus methods for testing. Methods are specified or cited in the compliance program and compendiums, or by the customer. In some cases, testing and procedures as established by the instrument manufacturer are used.
2. Sample handling and management procedures to maintain integrity of both the samples and the documentation to support the analytical data.
3. Maintenance of records in such manner that facilitates retrieving them later. Records are maintained in the analyst worksheet packet or web application by sample number. Records may be archived on- or off-site depending on the home division of the collector or in a web application. Archival retention periods are stated in the laboratory’s record management procedure and are in accordance with the agency’s established record retention schedule.
4. Employment of qualified and trained personnel to perform the tasks to support the laboratory objectives. Competency demonstrations by technical personnel conducting laboratory methods are conducted and documented.

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5. Routine maintenance of quality control data to support testing results by demonstrating that measurement processes are maintained in statistical control. Accuracy and precision control charts are used to monitor performance.
6. Maintenance of an instrument calibration program that provides measurement traceability to International System of Units (SI) units. This is accomplished with the use of national, international, or industry accepted standards of measurement.

ORS laboratory personnel follow the policies included in this Volume, the processes described in their local operating procedures, and the processes described in laboratory methods referenced in this Volume.

The sections in this Volume describe elements and reference procedures that outline the management system established to accomplish the mission of the laboratory.

- 8.2.2. The management system process and procedures as defined in this manual maintain the integrity of the management system for consistent operations when changes such as a change in the structure of the organization or management, or a change in a policy or procedure are made.

Primary consideration in all policies, procedures, and objectives is given toward retaining personnel competence and impartiality.

- 8.2.3. The policies for operation of the laboratory management system are established to address the requirements of ISO/IEC 17025:2017. ORS laboratories are committed to laboratory accreditation per the requirements of ISO/IEC 17025:2017.

The implementation of the quality policies is evidenced by the way work activities are conducted. Implementation of the management system procedures is evidenced by the generation of required records. The audit and management review activities are the mechanisms that are used to monitor the implementation effort of the laboratory management system.

Evidence of management's commitment to the management system and its continual improvement in effectiveness is demonstrated by but not limited to participation of managers in the management reviews, performance of internal audits, proficiency testing, and the analysis of quality control samples.

- 8.2.4. Management system procedures supporting quality policies are cited in the Related Procedures/References at the end of each section of this Volume.

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Where needed, each laboratory shall have procedures to implement the quality policies at the local level and include these procedures in the document control system. All documentation, processes, systems, records, related to the fulfillment of the requirements of ISO/IEC 17025:2017 shall be included in, referenced from, or linked to the management system.

- 8.2.5. All laboratory employees involved in laboratory activities have access to approved and controlled consensus standards, instrument manufacturers' manuals, and procedures for reference ensuring consistent application and validity of activities that contribute toward results reported.

8.3. Control of Management System Documents (Option A)

- 8.3.1. Changes to management system documents are made per the laboratory document control procedure and involve periodic revisions of this Volume.

The operational procedures for ORS laboratories are controlled as described in ORA-LAB.4.3 *Document Control and Management*.

The document control and management procedure describes the process for controlling quality documents that form part of the laboratory management system. The quality documents include those required for the generation of laboratory data. These documents include those published by the laboratory and those published externally. Documents of external origin include regulations, standards, test methods, instructions and manuals.

Control of electronic management system documents and data is addressed in section 7.11.

- 8.3.2. Document control requirements:

- A. Documents issued to personnel in the laboratory as part of the management system are reviewed for adequacy and approved by authorized personnel prior to issue in accordance with ORA-LAB.4.3 Document Control and Management procedure.
- B. Documents are reviewed per an established schedule and revised as necessary to ensure continuing suitability and conformance with the management system and ISO/IEC 17025:2017 requirements. These reviews should include an assessment of reference documents and pertinent background information.
- C. Altered or new text is identified either in the document, document change history section, on a cover page, redline file, or in attachments. Changes can be described in general terms since the details can be demonstrated in the archived document. Document revision is recorded on each document and tracked within QMiS.

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- D. Authorized management system documents and external documents are available at locations where operations essential to the effective functioning of the laboratory are performed. Distribution and locale of these documents is controlled.
- E. A document control header as described in the document control and management procedure uniquely identifies management system documents generated by the laboratory. Such identification includes the revision status, identification number and inclusive pagination.
- F. The unintended use of obsolete documents is prevented, and suitable identification is applied to them if they are retained for any purpose.

8.4. Control of Records

- 8.4.1. ORS laboratories maintain records according to *ORA-LAB.4.13 Record and Data Management* to sustain objective evidence showing fulfilment of the requirements of the quality system. These records are required to be legible and readily identifiable for retrieval.
- 8.4.2. Retention time, archival, and disposal of ORS Laboratory records are in accordance with SMG 3291.1 Records Management Policy and existing FDA and ORA record retention schedules.

Quality record storage and protection are maintained in QMiS or recorded within each laboratory's individual records file plan.

Internal access to records is controlled through various methods, such as, but not inclusive of, password protected storage, both electronic and physical, provided to authorized personnel to maintain confidentiality. Access from entities outside FDA is governed by statutes within the Freedom of Information Act (FOIA) July 4, 1966, President Obama's Freedom of Information Act Memorandum dated January 21, 2009, and Attorney General Holder's Freedom of Information Act Guidelines, March 19, 2009.

Additional requirements regarding technical records are addressed in section 7.5 and control of electronic records is covered in section 7.11 of this document.

8.5. Actions to Address Risks and Opportunities

- 8.5.1. Top management in each ORS Laboratory meet regularly to assess risks and opportunities associated with all laboratory activities to:
 - A. Assure the management system achieves its intended results;

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- B. Enhance opportunities to achieve the purpose and objectives of the laboratory;
- C. Prevent, or reduce negative impacts and potential failures in laboratory activities;
- D. Achieve improvement

Examples of areas evaluated consist of the following, although the list is not all inclusive:

1. Turnaround times for data reporting
2. Training and competency
3. Structure to ensure impartiality of personnel
4. Equipment issues
5. Program requirements
6. Facilities/Environment
7. Effectiveness of corrective and preventive actions
8. Outcomes of internal audits
9. Complaints
10. Processes to ensure confidentiality

8.5.2. Plans, final evaluation, actions and implementation of actions, improvement, and assurance of intended actions are outlined in section 8.9 Management Reviews.

8.5.3. Actions taken to address risks and opportunities are proportional to the potential impact on the validity of laboratory results.

8.6. Improvement

8.6.1. The effectiveness of the laboratory's management system is improved by using the following activities: internal audits; management reviews; analysis of quality control data; corrective actions; preventive actions (see ORA-LAB.4.12); the quality policy; and the quality objectives.

8.6.2. The laboratory seeks customer feedback on their services and general performance. Records of the comments, both positive and negative, are maintained and are considered for identifying management system improvements during reviews performed by laboratory management.

8.7. Corrective Actions

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Each ORS laboratory designates the authorities for implementing corrective action when one of the following is identified:

- A. non-conforming work,
 - B. departures from the policies and activities outlined within the management system, and
 - C. departures from required technical operations.
- 8.7.1. When a non-conformance is identified, the corrective action chosen addresses the magnitude of the non-conformance and the risk attributed to the non-conformance.
- A. Immediate action is implemented to correct a nonconformity and address the consequences..
 - B. An evaluation is performed to determine the cause(s), a history of similar issue(s), potential for recurrence, and the need for action to eliminate the problem to prevent recurrence.
 - C. Corrective actions are determined and implemented based upon this evaluation.
 - D. A review of the effectiveness of corrective actions is performed.
 - E. If necessary, updates for risks and opportunities are determined during planning.
 - F. Essential changes discovered during the corrective action investigation are implemented within the management system, where necessary.
- 8.7.2. Corrective actions are appropriate to the effects of the nonconformities encountered.
- 8.7.3. Corrective actions are recorded, to include the nature of the nonconformities, cause(s) and subsequent actions taken, including the results of any corrective action.

Related Procedures/References

- ORA Laboratory Manual, Volume II, ORA-LAB.4.11 Corrective Action

8.8. Internal Audits

8.8.1. General

Internal audits are conducted according to a schedule included in the laboratory's audit procedure. Internal audits are conducted of activities to verify that operations continue to conform to the requirements of the management system and ISO/IEC 17025:2017.

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An internal audit process is used to evaluate the effectiveness of the management system established for laboratory operations.

8.8.2. Audit Program

- A. The internal audit program is defined in ORA-LAB.4.14 Audits. The program takes into consideration the importance of the laboratory activities concerned, changes affecting the laboratory, and the results of previous audits.
- B. The QSM defines the audit criteria and scope for each audit in an audit plan.
- C. Results of the audits are reported to laboratory management.
- D. When audit findings cast doubt on the effectiveness of operations or the correctness or validity of the laboratory's test or calibration results, the laboratory implements appropriate correction and corrective actions in a timely manner according to ORA-LAB.4.11 Corrective Action.
- E. The area of activity audited, the audit findings, and corrective action that arise from them are recorded according the laboratory's audit procedure.

Related Procedures/References

- ORA Laboratory Manual, Volume II, ORA-LAB.4.14 Audits.
- ORA Laboratory Manual, Volume II, ORA-LAB.4.11 Corrective Action.

8.9. Management Reviews

A management review is conducted by the laboratory's executive management at least once each fiscal Year; however, can be conducted more often according to planned intervals determined by each ORS laboratory.

This review is conducted to ensure continuing suitability, adequacy, and effectiveness based upon information related to the inputs and outputs of laboratory activities and operations and stated policies and objectives.

Related Procedures/References

- ORA Laboratory Manual, Volume II, ORA-LAB.4.15 Management Review

9. Document History

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Revision #	Status* (D, I, R)	Date	Author Name and Title	Approving Official Name and Title
1.2	R	1/19/2005	LMEB	LMEB
1.3	R	4/29/2005	LMEB	LMEB
1.4	R	11/10/2005	LMEB	LMEB
1.5	R	11/15/2007	LMEB	LMEB
1.6	R	6/6/2008	LMEB	LMEB
1.7	R	2/2/2010	LMEB	LMEB
1.8	R	2/6/2013	LMEB	LMEB
1.9	R	1/22/2013	LMEB	LMEB
2.0	R	5/2/2014	LMEB	LMEB
03	R	08/13/2019	LMEB	LMEB

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

10. Change History

Revision #	Change
1.2	Table of Contents – added Document History, page 44 Section 4.2.4, page 10, second bullet item – (technical management) added to Responsible Managers
1.3	Section 4.1, Organization, I. Principal Responsibilities, page 4 - added PHS Act. Section 4.4.3, page 13 - Volume I Subsection 4.5. title changed from "Subtracting of Tests" to "Subcontracting of Tests". Section 4.11.2, page 19, first bullet under Related Procedures - added the word "has". Section 5.2.1, page 25, second paragraph - changed Office of Regional Management to Office of Resource Management. Section 5.4.2, Selection of Methods, page 29, first paragraph - added after LIBS "that are included in compliance programs and special assignments." Section 5.4.5.2., page 30 - corrected "amplifications" to "applications".

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Revision #	Change
1.4	Quality System and quality system references changed to Management System and management system throughout document. Table of Contents – page column renumbered Section 1.0, changed date to 2005. Section 4.12, add “assignments” to fourth bullet. Section 4.1.5 a., page 4, added second sentence. Section 4.1.5 d., page 5, website updated. Section 4.1.5 k., page 6, added. Section 4.1.6, page 6, added. Section 4.2.2 c., page 10, added last sentence. Section 4.2.3, page 10, added new and moved former 4.2.3. to 4.2.5, page 10. Section 4.2.4, page 10, added new and moved former 4.2.4 to 4.2.6, page 10. Section 4.2.7, page 11, added. Section 4.7, page 17, renumbered with 4.7.1 and added 4.7.2 Section 4.15, Improvement, added to Table of Contents and page 24. Section 5.2.2.1, page 26, added last sentence to third paragraph. Section 5.9, page 41, renumbered with 5.9.1 and added 5.9.2; added ORA laboratory procedure for handling control of non-conforming work to Related Procedures. Section 5.10.9, page 44, revised.
1.5	Table of Contents – Improvement moved to 4.10 & elements moved down; page column renumbered Section 4.1.5 d., page 5, website updated. Section 4.2.2, page 7, FDA mission statement deleted & ORA mission statement added; revised second sentence Section 4.2.2 e., page 10, revised second sentence. Section 4.3.2, page 12, corrected number to 4.3.3 Section 4.10, page 18, corrected to Improvement to align with ISO 17025:2005 Section 4.11-4.15, pages 19-23, moved elements down one to align with ISO 17025:2005 Section 4.7, page 17, renumbered with 4.7.1 and added 4.7.2

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1.6	Section 4.1.5 i. and j – Quality Management System Manager changed to QSM Section 4.2.6 – Quality Manager changed to Quality System Manager Sections 4.1, 4.11, 4.12, 4.13, 4.14, 4.15 – Related Procedures, numbering corrected for procedures Section 4.8, 4.9.2, 4.11.5 – numbering corrected for procedures Section 5.9 Related Procedures – updated websites Version 1.7 changes: Section 4.15 a. and f. - updated Section 4.15 d. – web link updated Section 4.1, Related Procedures – deleted first bullet Section 4.2.2 b. – third bullet revised Section 4.2.5 – changed “Volume” to “Manual in last sentence Section 4.3.2.2 d. – revised Section 4.3.3.1 – revised Section 5.2.4 - revised Section 5.2.5 – changed “Director” to “Management” Section 5.4.2 – added last sentence to first paragraph Section 5.5.7.1 – revised Section 5.5.9 - revised Section 5.9 related Procedures – web links updated Section 5.10.4 - revised Footer – web link updated
1.7	NOT DOCUMENTED

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Revision #	Change
1.8	Section 4.1 I. – changed Associate Commissioner for Regulatory Affairs to Office of Regulatory Affairs Associate Commissioner Section 4.1.3 – changed “addresses” to “locations”; changed SMG 1300 to 1300.1 through 1316.4 Section 4.1.4 - changed SMG 1300 to 1300.1 through 1316.4; added “About FDA” Section 4.1.5 d. – updated weblink Section 4.1.5 e. - changed SMG 1300 to 1300.1 through 1316.4 Section 4.1.5 f. – added Rockville and changed (HHS) to (RHRC) Section 4.1 – Related Procedures – added ORA-QMS.007 Section 4.3 – Related Procedures – added ORA-QMS.001 Section 4.4.1 – changed FMD17B with ORA-ORM.003 in last sentence of last paragraph Section 4.4 – Related Procedures – deleted FMD 17B; added ORA-ORM.003 Section 4.5.1 – changed FACTS Manual to LM Volume III, Section 2 Section 4.5 – Related Procedures - changed FACTS Manual to LM Volume III, Section 2 Sections 4.5, 4.8, 4.9, 4.11, 4.12 – Related Procedures – added applicable ORA-QMS procedure Section 4.13.1.3 – changed “process” to “requirements” in third sentence Sections 4.13, 4.14, 4.15 – Related Procedures – added applicable ORA-QMS procedure Section 5.2.2.1 – changed “by” to “in accordance with” Section 5.5.11 – reformatted number Section 5.8 – Related Procedures - deleted FACTS Manual Section 5.9 – Related Procedures – updated weblinks Section 5.10.3.1 c. – reworded
1.9	Division of Field Science changed to Office of Regulatory Science throughout DFS changed to ORS throughout Office of Regional Operations changed to Office of Operations throughout ORO changed to OO throughout Section 5.9.2 – Related Procedures – SOP numbering series revised and websites deleted
2.0	1.0– deleted “2005” 4.13, 4.14, & 4.15 e. – changed Sections 1300.1-1316.4 to Volume I, Section 1300 4.15 a. – deleted OPM manual reference and added OPM website 4.2.2 b. – added web application and added to last sentence on 3rd bullet 4.3.2.3 – revised 1st paragraph 4.13.1.2 – revised 4.13.2.1 – added “and/or LIMS” 5,8.3, 5.10.1., 5.10.2., & 5.10.5 – added reference to LIMS
03	All section numbering and content updated to reflect changeover from ISO/IEC 17025:2005 revision requirements to 2017 version requirements