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1. Introduction

As the regulatory agency designated to maintain the safety of the nation's foods, drugs, biologics, medical devices, tobacco and radiological health products, FDA has broad responsibilities to protect the public health. It is the vision of the Office of Regulatory Science (ORS) to provide a defensible and prevailing scientific, research and analytical base for regulatory decisions that protect and promote public health. Vital to carrying out this mission is the continual development, validation and improvement of methods that support our regulatory responsibilities. The ORS Method Development and Validation Program (MDVP) is designed to satisfy the need for regulatory analytical methods meeting current and anticipated public health program needs and agency priorities through collaboration across the FDA Centers and ORS Laboratories. Furthermore, ORS Laboratories must continue to maintain good laboratory practices through necessary quality assurance and regulatory requirements. The exploration of new technologies and methods for rapid analyses, as well as modernization of existing methods to achieve higher efficiency or broader scope, are also important components of this science program.

2. Purpose

The goal is to satisfy the need for regulatory analytical methods meeting current and anticipated public health program needs and agency priorities.

This ORA Laboratory Manual section provides the procedures for the identification, development, submission, review and publication of method protocols, validation studies, method extensions or other research studies. The procedures assure projects meet regulatory needs, accomplish their intended purpose, include validation for Agency-wide distribution (where appropriate and/or in conjunction with the appropriate Centers), and become meaningful analytical tools. Additionally, it provides scientific guidelines for the program and encourages and enhances the creative skills of talented scientists in ORS Laboratories.

3. Program Overview

ORA's program alignment that took effect in 2017 led to the creation of ORA's first office dedicated to leadership and management of research: Office of Research Coordination, Evaluation and Training (ORCET) within ORA's Office of Regulatory Science (ORS). Method development and validation efforts comprise most of the research activities within ORS and are managed by ORCET.

3.1.1. Program Goals

The goals of the Method Development and Validation Program are the following:

A. Provide opportunities for ORS scientists to develop analytical methodologies and expertise that support the regulatory and public health protection mission of FDA and solve continuing, new, or emerging regulatory problems;

B. Support FDA Center research through method validation and collaboration with FDA Center scientists;

C. Revise existing methods to use improved instrumentation or technology and validate methods to "Standard/Official" method status for FDA use;

D. Incorporate the developed methods into routine regulatory operations; and to transfer the technology, where appropriate, to our stakeholders and customers; and

E. Develop the knowledge, investigative skills, and abilities of ORS staff analysts.

3.2. ORS Method Development and Validation Program

3.2.1. ORS Planned Method Development and Validation Studies

Planned development of methods and studies are designed to address regulatory program analytical testing problems. Designated full time employee

(FTE) resources are allocated in the annual ORA work plan for these method development and validation activities. The method or analytical need can be conceived by ORS headquarters in communication with Centers, ORS analysts, Food Emergency Response Network (FERN), and Science Advisors. ORS Lab Directors will be responsible for resource management (personnel, funds, equipment) to perform planned method development and validation activities. The outcome of method development and validation work may directly affect Center regulatory program development and implementation.

3.2.2. Compliance Program Directed Method Development and Validation

Method development and validation operations mandated in compliance programs are planned in the Centers, conducted by ORS labs and monitored by ORCET. The ORS analyst(s) assigned to the project have latitude to plan activities to explore and solve the problem and can ask for input from ORCET; ORCET will define the parameters for the scope of the study and provide final approval on the study.

Laboratory Management coordinates local method development/validation activities with ORCET. ORCET communicates with appropriate Center regarding criteria for validation.

Foods Program multi-laboratory method validation activities are coordinated through the Research Coordinating Groups under the Foods Program Regulatory Science Steering Committee (RSSC). ORS members are represented on these Research Coordinating Groups and provide their review and feedback as part of the RSSC process.

3.3. Other Programs Available to ORS for Method Development and Validation

Some methods are developed and validated in real time in response to an emergency or a product related adverse event or based on a consumer complaint. Method development and validation ideas and priorities can also be derived from various ORA/Center Scientific Steering Committees (ORA/CDER Strategic and Scientific and Compliance Steering Committee, ORA/CDRH Strategic and Scientific and Compliance Committee, Center for Tobacco Products, agency-wide initiatives identified by FDA Office of the Chief Scientist, intramural grant opportunities, and through the Nanotechnology Program).

3.3.1. Directed Method Development and Validation

In each ORS laboratory's annual work plan, a specified number of hours are assigned per operational scientist to plan and complete method development and validation needs that arise during the year and not covered by other programs.

New method development work will be identified and specified by ORCET. The ORA Laboratory Manual policies and procedures applicable to method development and validation are followed as well as applicable technology requirements and local procedures. This work is operationally controlled by local management, approved, coordinated and evaluated by ORCET. Utilization of all specified number of hours assigned to research activities within the ORS laboratories is ultimately the responsibility of ORCET in order to promote mission-relevant research within the ORS laboratory network.

3.3.2. ORS Research Center Method Development and Validation

In the early 1980s, ORS research centers were established in several ORS laboratories to focus research efforts in support of a variety of program areas. Three ORS research centers remain: The Applied Technology Center (Bothell, WA), Animal Drugs Research Center (Denver, CO), and Total Diet and Pesticide Research Center (Lenexa, KS). ORS Laboratory Network also includes two specialty Labs and two specialty groups: Winchester Engineering and Analytical Center (Winchester, MA), Forensic Chemistry Center (Cincinnati, OH); Atlanta Tobacco Products Lab (Atlanta, GA), and the ORA-NCTR Nano Core Facility (Jefferson, AR). The ORS research centers provide complex analytical support to ORS laboratories and the Centers, conducting research on current methodology; developing and refining new rapid chemical and biological methodology; conducting and participating in collaborative studies and validation trials of analytical methods; and providing expert technical scientific assistance and consultative services.

Each ORS Research Center will develop a research plan in consultation with ORCET that aligns with Center and Agency priorities. Projects are defined through planning meetings with the research centers and ORCET. Projects are selected to support existing regulatory needs and are tracked for progress and impact via CARTS.

3.3.3. Science Advisor Program

The Science Advisor is a special government employee and serves as a consultant to the specific FDA/ORA/ORS Laboratory. The Science Advisor reports directly to the Lab Director and advises management (local and headquarters) on scientific issues as they relate to the regulatory operations of the unit. Science Advisors provide scientific expertise in many areas including methodology, training, new technology, instrumentation, research, literature searches, publications, etc. Science Advisors work formally and informally with analysts, researchers, Supervisors, Branch Directors, Laboratory Directors,

ORCET, and the Science Advisor Working Group to assist in formulating research objectives and goals.

The Science Advisor is responsible for understanding and keeping abreast in the major areas concerning regulatory responsibilities and policies of the Agency as they relate to the unit he or she serves. To accomplish this, Science Advisors must acquire and maintain knowledge of the major thrusts of the agency/district/region and areas of scientific expertise to appropriately provide overall guidance on field research efforts. The Science Advisor assist in keeping the local research program on track, i.e. providing technical guidance/troubleshooting advice to researchers, working with ORCET to ensure research aligns with current agency needs, ensuring the technical accuracy of CARTS proposals, abstracts, presentations, and research publications, identifying needs for major instruments and equipment. The Science Advisor also will occasionally review CARTS proposals, abstract, presentations, and research publications from other ORA/ORS laboratories when they fall within the Advisor's area of expertise.

The major areas of involvement of Science Advisors in ORA/ORS laboratories are as follows:

<u>Coordination of Research Activities</u>

- Provides input to ORCET on ORA/ORS field research needs
- Guides analysts in developing high quality CARTS proposals and grant proposals
- Assists in literature searches on the research topics
- Reviews CARTS proposals and recommends changes as necessary
- Assists in critical thinking and troubleshooting during the actual research period as necessary
- Assists researchers in analysis of data and interpretation of results
- Ensures researchers developing new methods conduct validations that meet relevant guidelines

- Assists researchers in the preparation of CARTS progress and final reports

- Advises researchers and management and facilitates preparation and submission of abstracts, presentations, and manuscripts

- Co-authors papers and presentations, where appropriate, when contributions meet relevant authorship guidelines.

- Monitors schedules for the research progress timelines: ensures final approval of CARTS proposals prior to initiating research, assists in timely submission of CARTS progress reports and final reports, assists in timely abstract submission to facilitate clearance prior to deadlines, etc. and is a conduit for keeping the research program on track

Science Advisors are special government employees (SGE) and therefore their time reporting is governed by special rules. Up to one Science Advisor FTE may be assigned to each ORS Laboratory. ORCET will leverage science advisors as an enterprise-wide resource and oversee renewals to ensure maximum utilization of their expertise.

ORS Headquarter Science Advisors report to ORCET. ORS Laboratory Science Advisors report to local lab management; however, ORCET will coordinate their selection and evaluation for continued service to ensure their expertise remains impactful and aligned to Center and Agency scientific initiatives.

3.3.4. Cooperative Research and Development Agreement

The Federal Technology Transfer Act of 1986, (FTTA), authorizes government agencies to enter into collaborations with the private sector, academic institutions, and other organizations. The mechanism used is known as the Cooperative Research and Development Agreement (CRADA).

A CRADA is used to formalize a specific collaborative project which may involve research leading to new inventions or further development of existing government or non-government inventions in fulfillment of FDA missions. The primary purpose is to transfer the technology and intellectual property to the commercial marketplace. The terms of a CRADA, which are negotiated by FDA and the collaborator, may address patent rights and licensing matters as well as the collaborative research project.

A CRADA is not intended to be a general funding mechanism. CRADA-derived funds are to be used for costs associated with the project specified in the CRADA. Laboratories must be prepared to address the impact to ongoing

research if a CRADA and related financial support is terminated unexpectedly. Time allotted to a CRADA project can be taken from a laboratory's discretionary time, planned research allotment, or by agreement with a Center to use other compliance program planned time.

More information can be obtained at the Science First Homepage under FDA Scientific Resources FDA Technology Transfer Overview

All ORS Laboratory CRADA activities will be overseen by ORCET. Labs are required to develop a new CRADA in consultation with ORCET as well as engage with ORCET on renewal of existing CRADAs.

4. Roles and Responsibilities

4.1. Associate Commissioner for Regulatory Affairs (ACRA) and Director of Office of Regulatory Science (ORS)

The Associate Commissioner for Regulatory Affairs and the Director of Office of Regulatory Science share responsibility for promoting and supporting a strong ORS method development and validation program as part of ORS research as well as determining ORS scientific goals.

4.2. Foods Program Regulatory Science Steering Committee

FDA Foods Program Regulatory Science Steering Committee (RSSC) operates under the sponsorship of FDA Foods Program Governance Board and is composed of members from the Office of Regulatory Affairs (ORA), Center for Food Safety and Applied Nutrition (CFSAN), and the Center for Veterinary Medicine (CVM) which are the agency components that perform regulatory and scientific work in the foods area. Chairmanship of RSSC rotates between ORA, CFSAN, and CVM annually.

The primary function of the RSSC is to coordinate scientific research and method development activities among CFSAN, CVM, and ORA to ensure research projects are not duplicated; appropriate collaborations on scientific projects are facilitated; and standardized scientific processes, where feasible, are established. Key components of the mission include:

- Promoting individual Center and ORA strategic science plans and coordinating Center/ORA cross-cutting research portfolios, so that projects are complimentary, not redundant nor conflicting; proposed scientific work builds upon previous explorations, findings, recommendations and is supported by current FDA policy; collaborations are leveraged when appropriate; and individual foods program unit and agency scientific mission priorities are upheld;

- Developing and implementing a risk-based approach to identifying and coordinating new research areas of common scientific interest;
- Maintaining a unified analytical methods development, validation and implementation program that is mission-aligned;
- Identifying new technologies that can be leveraged in analytical work, advocating investigation of such new technologies via research, and facilitating integration of newly developed methods into foods program scientific work;
- Generating a candid forum where effective horizon scanning can be performed to identify pro-active steps that can be taken by the foods program scientific community to attain analytical readiness for future consumer safety threats in the foods program regulated areas.

4.3. Medical Product and Tobacco Centers (CDER, CBER, CDRH, CTP, CVM)

FDA Centers are responsible for providing strategic input regarding direction and priority of method development and validation respective of each Center's program area. Center procedures for carrying out such work should be incorporated into ORS MDVP.

4.4. Office of Regulatory Science (ORS)/ Office of Research Coordination Evaluation and Training (ORCET)

The Office of Research Coordination Evaluation and Training (ORCET) is responsible for the scientific management of ORS laboratories. As such, ORCET sets direction for the ORS method development and validation program and provides scientific support. ORCET issues the call for proposals, assigns reviewers and approves proposals, and maintains the approved and completed project list. Additionally, ORCET is responsible for tracking research progress, achievement of deliverables and evaluation of impact.

ORCET works with the Laboratory Directors, the Centers, and ORS analysts to guide and assist with the method development and validation process. The Director of ORCET is the recommending and approving official for ORS laboratory method development and validation programs documented in CARTS. ORCET is responsible for directing, monitoring, and coordinating ORS research, inclusive of all method development and validation and implementation activities across the entire ORS Laboratory Network.

4.5. ORS Laboratory Management

Laboratory Management includes supervisory personnel with titles that may include Laboratory Director, Branch Managers, and Supervisors. Operational management of the ORS method development and validation resources reside at the local laboratory management level. The Laboratory Director is responsible for providing resources and ensuring implementation of

procedures. Other management personnel are responsible for implementing the procedures. Laboratory management is responsible for developing and executing their laboratory's approved method development and validation program. This includes: assuring that relevant expertise and proficiency exists at the lab to support a proposed project, necessary equipment is available, all facility needs are properly evaluated and addressed, and FTE resources are available to conduct the project without impacting the lab's programmatic testing obligations. Timely planning, direction, and accomplishment of these projects are crucial. Laboratory Directors rely on supervisors, quality managers, senior laboratory staff, and Science Advisors and can consult with ORCET regarding any challenges and issues.

Laboratory management must establish an environment where there is vigorous growth, development, and accomplishment of projects within the laboratories. Recognition that is commensurate with the level of contribution to the regulatory mission of ORS and FDA by scientists who successfully complete method development and validation projects is an important aspect of a successful program.

Laboratory Management (namely, Supervisor, Branch Director and Lab Director) are assigned the first three levels of approval in CARTS and are responsible for thoroughly reviewing any submitted MDVP projects for mission-relevance, technical merit, feasibility, and resource utilization before providing concurrence. Last two levels of approval in CARTS belong to the in-depth technical/program reviewer and ORCET Director/Deputy Director.

4.6. Quality Managers

The ORS Headquarters and ORS Laboratory Quality Managers are responsible for ensuring the ORA Laboratory Manual, ORS-level directives, and local laboratory procedures are implemented to ensure traceability and defensibility of data provided for method development and method validation in accordance with maintaining accreditation. ORS Quality Managers also serve as resources to provide input on questions related to formal validation/verification protocols, document practices, statistical analyses of data, or study design. ORS Quality Managers can consult with other experts to provide thorough responses on such questions that may arise at the laboratory.

4.7. ORS Analysts

ORS analysts are responsible for the following:

A. Following the ORA Laboratory Manual procedures, ORS-level directives, local laboratory procedures, and any other procedures and/or guidance documents appropriate for the specific project

B. submitting method development and validation needs through local management in response to ORCET initiatives and/or programmatic needs.

C. developing and submitting proposals in accordance with the approved procedures;

D. timely accomplishment of approved projects;

E. adhering to the highest standards of intellectual honesty and ethical standards in formulating, conducting, and presenting method development and validation work; and

F. following Agency level and ORCET research and publication requirements and guidelines

G. submitting new proposals into CARTS and tracking timelines and milestones in CARTS.

4.8. Science Advisors

Science Advisors aid laboratory management and analysts by providing technical analytical guidance and method development and validation process guidance at the local level. More specifically, the advisors provide direction towards the development of concept and method development and validation project papers, and assist in the conduct, evaluation, and presentation of method development and validation end-products. They promote interaction and collaborations with their respective universities and other science advisors where appropriate, including outside partnerships.

Additionally, the science advisors recommend improvements towards the method development and validation program, provide periodic follow-up reports regarding method development and validation's regulatory impact including associated publications, presentations, collaborative studies, adoption as official methods by additional field and headquarters laboratories, and inclusion in compliance programs.

4.9. FDA Center Scientists

FDA Center scientists contribute to ORCET's planning and prioritization for method development and method validation projects for ORS laboratories. Center scientists will work through their appropriate ORA/Center steering committees to provide this input and will contribute technical guidance, scientific consultation/review, method documents, and validation protocols as requested by ORCET for projects included in the method development and validation program.

5. ORS Method Development and Validation Process

5.1. Laboratory Method Development and Validation Program (MDVP) Overview

The MDVP program supports five project categories:

5.1.1. Method Development

A. Projects are designed to develop, validate, and implement new methods.

B. Expected Outcome: A new method is implemented within a single laboratory or method validation proposal for field wide implementation.

5.1.2. Method Validation

A. Projects are designed to evaluate innovator validated methods via peer reviewed assessment and inter-laboratory collaborations.

B. Expected Outcome: Validated regulatory method for ORS lab wide implementation.

5.1.3. Method Modification, Enhancement, and Extension

A. Projects are designed to extend an existing method to one or more additional matrices, analytes or instrumentation; projects designed to improve an existing method.

B. Expected Outcome: Modified method implemented within the laboratory or method validation proposal for enterprise-wide implementation.

5.1.4. Technology Exploration

A. Projects are designed to investigate and evaluate the usefulness and applicability of new technologies and increase the analyst's base expertise in these new technologies.

B. Expected Outcome: New technology accepted by one or more publications summarizing experiments performed, data collected, and recommendations.

5.1.5. Applied Studies

A. Projects are designed to test hypotheses related to FDA mission such as food safety, quality mechanisms, contaminants, analyte/matrix interactions, metabolism studies, degradation/depletion studies, process effects, stability studies. Although method development may be a component of these projects, it is not the primary focus.

B. Expected Outcome: Study, results, and impact for FDA described in one or more publications.

The MDVP process is designed to increase flexibility and timely planning of quality projects that benefit the agency. Each ORS laboratory is required to have an ongoing MVDP plan commensurate with their method development and validation time allotment. A good program is mission related and does not duplicate research work being done elsewhere.

ORCET in collaboration with Laboratory management, quality managers, analysts, and Science Advisors have an important role in managing the program. Throughout the year, method development and validation progress and accomplishments are monitored, and adjustments made to react to emerging analytical needs as they arise. Laboratories are expected to fully plan and accomplish their assigned method development and validation time.

5.2. Method Development and Validation Program (MDVP) Procedures

5.2.1. ORCET Management of New Research

ORCET utilizes different mechanisms to identify research proposals that support core agency mission:

5.2.1.1. ORCET Priorities for Proposals:

ORCET, via its annual research summit, performs horizon scanning with ORS Laboratories and identifies regulatory gaps. ORCET also collects input from Centers and generates a list of the highest priority method development and validation projects that target validation, development, and enhancement of regulatory methods, capability building and technology expansion and shares with ORS laboratories as part of the ORCET research forum. Additionally, at that time, laboratories may also submit proposals for projects in areas not listed in the ORCET priorities based on what they perceive to be emerging needs. ORCET will evaluate all these submissions for mission-relevance, feasibility, and projected impact.

5.2.1.2. Lab-Directed Method Validation Proposal

ORCET can choose a laboratory to develop a method based on Center priorities and programmatic needs. The ORS lab scientist will work with ORCET and the relevant programmatic office (ORS/OFFLO or ORS/OMPSLO) to develop a method through the different topic areas as specified in section 5.1

5.2.1.3. Agency Level Call for Proposals:

As part of FDA's efforts to strengthen the science through innovation and to support regulatory decision-making, the Office of the Chief Scientist (OCS) puts out a yearly "Call for Proposals" to the intramural grant cycle program with the following five programs:

A. Chief Scientist Challenge Grants
B. Collaborative Nanotechnology (CORES) Grants
C. Medical Countermeasures Initiative (MCMi) Challenge Grants
D. Office of Minority Health Intramural Research Program
E. Office of Women's Health Intramural Scientific Research Funding Program

ORS Labs can collaborate with Center scientists or enter independently to develop a full proposal based on these program areas. The proposals are reviewed by ORCET prior to submission to OCS for the agency program review and awardee selection process based on scientific merit.

5.2.2. Proposal Preparation and Submission

Method development and validation for product commodities that fall under other Centers will follow the guidance in this document or appropriate Center SOPs. All proposals for projects to be considered must be initiated through the Component Automated Research Tracking System (CARTS). Project types may include method development; single laboratory method validation; multi laboratory validation; tech modernization project requiring new equipment; and method development and validation program funding for reagents. Refer to ORA-LAB.014, Component Automated Research Tracking System (CARTS) for detailed guidance.

ORCET will solicit specific proposals as needed and will manage laboratory research portfolio to support Agency needs.

All research proposals initiated in ORS Laboratories need to be submitted and tracked electronically in CARTS.

5.2.3. Proposal Review and Project Assignment

All proposals must be submitted through CARTS. After clearing local management review, ORCET performs the Headquarter review either internally and/or assigns the review to a scientist/science advisor in an ORS lab, at the ORS/OFFLO/OMPSLO group, or at a Center with expertise in the technology area. In-depth review consists of input from a technical reviewer

and input from a programmatic reviewer. Within 30 days of submission ORCET will complete the CARTS review.

Proposal review considers, but is not limited to, scientific merit (e.g. objectives are realistic and scientifically sound), relevance to ORA/FDA mission, FDA impact, literature background, technical and equipment capability of the proposing lab, budget, timeframe, improvements over existing methodology, accuracy and completeness of the submission, and likelihood of success.

5.2.3.1. MDVP Proposal Approval Process:

After proposals are received, ORCET will coordinate technical and programmatic review of each project. As part of its review, ORCET will seek input from the relevant Center as a stakeholder. Once the review is concluded, ORCET will either recommend the proposal for development, validation, or the proposal will be returned with comments to the investigators. In cases where ORCET finds the proposed project not feasible, ORCET will suggest alternate avenues of research to the investigators.

For approved projects, once the laboratory completes the research, they will present their data and conclusions through CARTS and other reporting mechanisms as appropriate for final evaluation.

ORCET will survey the investigators on completed projects to collect information on impact of the project. This survey will be performed at the one-year point after completion of the project to allow time for impact to develop. Impact can be peer-review publications that result from the project, use the of newly developed/validated methods in regulatory testing, incorporation of the newly developed/validated methods in compliance programs, use of the newly developed/validated methods in response to an adverse event or public emergency.

ORCET will work with the relevant program office (OFFLO/OMPSLO) and Center stakeholders via available steering committees to help integrate newly developed or validated methods into regulatory use. While not all projects in the MDVP will require full multi-laboratory validation for use, single-lab validation is required for use in regulatory testing.

5.2.4. Project Execution and Reporting of Accomplishment Hours

Projects are managed and executed at the laboratory. Project records shall be in accordance with the local laboratory validation procedure and ORA Laboratory Manual procedures; and the approved research proposal.

Reporting of MDVP accomplishment hours by ORS Labs per instructions below is mandatory (refer to SOP-000401 ORS Reporting Accomplishment Hours for additional information)

The recommended timeline and schedule for project completion is:

≤ 500 hours = 6 months

> 500 hours = 12 months

Upon project completion, a final project report shall be submitted through CARTS and other reporting mechanisms summarizing results and conclusions.

While all new method development and validation projects are expected to be entered into CARTS, simple verification activities may not need to be captured in CARTS if they do not represent a significant time investment. As a rule of thumb, any verification project that is expected to last longer than four weeks should be entered into CARTS.

The project status is provided through CARTS on a quarterly basis. Additional project updates may be provided by other means on the progress that has been made and the current status of the project. Quarterly updates, final reports and complete validation package, resulting publications/presentations (LIBs, journal articles, official methods, etc.) shall be appended to the project in CARTS. The report will also be updated to include regulatory impact, publications, presentations, collaborative studies, adoption as official methods (adoption by other field and headquarters laboratories), and inclusion in compliance programs. CARTS tracking is instrumental in providing performance metrics, data on assessing return on investments and assisting ORS Managers in future planning. ORCET may also collect information from PIs on long-term impact by conducting surveys after one-year following completion of a CARTS project.

5.2.5. Presentation, Assessment, and Implementation

The basic product of scientific research is information. Dissemination of information ensures others interested in the problem can use the data. To accomplish this, ORS encourages and supports several types of research products. All such research products as defined in the section below must be submitted to ORS/ORCET for scientific evaluation and approved by ORCET for dissemination. All publications submitted for clearance must have supporting material (data package) readily available for review by manuscript reviewers upon request.

Authors are expected to produce manuscripts that are coherent, scientifically sound, and likely to be accepted for publication. Publications may include, but not limited to the following:

5.2.5.1. Scientific Articles

The FDA encourages various publication avenues such as peer-reviewed journals, book chapters, compliance programs, compendiums, etc. Manuscripts for these types of publications must be reviewed and approved for technical correctness; and adhere to Agency policy for review and clearance (Section 6.2). Local management is responsible for funding any page charges and ordering reprints. The ORCET Automated Manuscript Submission Portal should be used for clearance of these kinds of scientific output.

5.2.5.2. Laboratory Information Bulletins

Laboratory Information Bulletins are internal FDA publications. Overtime the purpose and usage of LIBs has evolved. LIBs are currently used to disseminate work at various levels of completeness; therefore, it has become increasingly important to specify the level of completeness the work represents. Some LIBs report 1) preliminary, original work to claim first ownership; 2) single laboratory validation; 3) multi laboratory validation. LIBs may be used for regulatory work as long as they have been fully validated following appropriate requirements. If the LIB represents un-validated work, the LIB shall include a disclaimer that the user must validate the method properly before use. This disclaimer is addition to the generic LIB disclaimer that all LIBs should bear.

Implementation of LIBs for regulatory use at ORS Laboratories requires full validation if the LIB has a disclaimer detailing that the work is un-validated; and initial implementation (verification) for fully validated LIBs. If a laboratory participated in the multi lab validation and its data was accepted for inclusion in the publication that data can count towards initial implementation.

Draft LIB manuscripts must be reviewed and approved by the Science Advisor (if applicable), Laboratory Director, Laboratory Management, and Quality Manager, before submission for publication.

The LIB review process is described in ORS.005 Laboratory Information Bulletins. All LIBs should be submitted to the ORCET automated manuscript portal for clearance.

5.2.5.3. Presentations and Posters

Results may be presented at scientific meetings as oral presentations or posters. Review and clearance of the presentations is in accordance with Agency and ORS policy. Currently, all ORA presentations are submitted and cleared through the ARTS system except for those presentations that will be delivered at an ORA-only forum.

5.2.5.4. Patent Application & Licensing

If the intellectual property produced by authors has potential for patent application or licensing, the Laboratory Director and the Principal Investigator should contact ORCET for information on their willingness to license the discovery to partners interested in commercializing the technologies.

FDA Technology Transfer - Licensing of Inventions

5.2.5.5. Pilot or Proof of Concept Studies

New areas of method development may become basis for new projects (e.g. validation studies) and may be listed in the next call for proposals. Enough records and reports are needed to support new projects and should be incorporated into existing CARTS process to capture reports.

5.2.5.6. Scientific Professional Membership Role

Involvement in scientific professional activities outside of the Agency will need to be cleared by ORCET. Examples of such activities could include, but not limited to:

A. Referee in an AOAC study
B. Representation in a Standards committee
C. Representation in a USP Expert Committee
D. Journal Editor
E. Invited speech engagements

5.2.5.7. Assessment and Implementation

ORCET, in conjunction with the appropriate Center, established ORA/Center steering committee or headquarter offices, and with ORS laboratory management input, can determine how methods are to be implemented. Methods can be implemented through compliance programs, FERN exercises, and Center assignments. New or improved methods, validated methods, adoption of new technology or rapid methods can be implemented field wide.

6. Scientific Conduct When Performing Research

ORS analysts are responsible for adhering to the highest standards of intellectual honesty and ethical standards when formulating, conducting or presenting method development/validation, studies or research. ORS scientists are expected to follow the guidelines below. The guidelines promote uniform application of the highest ethical standards when conducting research. Violation of these guidelines can undermine trust and confidence in the author's work

which in turn can undermine the public's trust in the Agency. Please consult Agency "Policy for Responding to Allegations of Research Misconduct" SMG 9003.1 and "Scientific Dispute Resolution at FDA" SMG 9010.1. for additional information.

6.1. Data Management

Data from analysis, studies, instrument data, and statistical data is recorded with integrity and is inseparable from the acquisition.

All data generated is recorded directly, promptly and legibly.

Data is retained by the laboratory to allow analysis and repetition by others. The schedule for retention is included in the ORA Laboratory Manual, Volume II, ORA-LAB.4.13 Record and Data Management and local laboratory's procedures.

Per agency requirements, all new projects need to outline an associated data management plan (DMP) that details how data generated as part of a project is going to be organized, managed, and stored. Implementation of DMP was necessitated by the exponential increase in volume of data generated from new scientific instruments such as whole genome sequencing.

6.1.1. Ensuring public access to Agency funded work:

On February 22, 2013, the White House Office of Science and Technology Policy (OSTP) issued a memorandum to executive departments and agencies to increase the public access to research funded by the Federal Government. The memo entitled "Increasing Access to the Results of Federally Funded Scientific Research" (OSTP Memo or Public Access Memo) directed federal agencies to maximize public access to digital data resulting from funded work. The FDA has developed guidance documents in accordance with the OSTP Memo and other executive and Office of Management and Budget (OMB) memos. This FDA guidance can be found in SMG 2126.4, Plan to Increase Access to Results of FDA-Funded Scientific Research and User Guide for Public Access to FDA-Funded Research. ORS Labs must follow Agency wide publication clearance practices outlined in Staff Manual Guide (SMG) 2126.3. The diagram below summarizes aspects covered in SMG 2126.4. It is the responsibility of the author to ensure all publications are publicly accessible following the procedures outlined in the preceding guidance documents.
Publication Practices

Publication is an integral and essential component of method development/validation, studies or research.

Authors are responsible for selecting the most appropriate mechanism for dissemination of their scientific work. Among criteria to be considered are target audience, application of the work, value to FDA's mission, and impact on public health. The landscape of scientific journals has grown tremendously in recent years, and thus, has presented the submitting author with many options in which to choose. In an effort to increase the visibility and elevate the scientific quality of research/method development studies conducted in ORS labs, ORCET strongly encourages considering the Impact Factor (IF) when selecting a journal. IF ratings can be found on the internet for various scientific disciplines using different algorithms. While it is understood that many factors must be considered in selecting a journal, IF can provide a valuable indicator on quality and reach of the publications found in that journal. Page or publication charges may, or may not, be associated with the journal, however, it is stressed that the quality and reputation be considered foremost when selecting a journal to best represent the work of FDA scientists. Journal charges for publication must be supported out of the local laboratory operating budgets.

For U.S. Government Employees, if published work is within the scope of their employment duties, then work is considered to be public domain, not subject to copyright protection and no copyright transfer is necessary. It is the responsibility of the author to be knowledgeable in this respect.

Authors are responsible to produce publications that are accurate, well written, not in conflict with Agency's position, and do not disclose trade secrets, confidential commercial information, or other non-public information.

Timely publication of new significant results is important for the progress of science, but fragmentary publication of the results of a scientific investigation or multiple publications of the same or similar data are inappropriate.

Information that would be necessary for scientific peers of the author(s) to repeat the study should be in each paper or made available from the author(s).

It is the analyst's responsibility to ensure that the scientific article is accurate, carefully researched and contains appropriately referenced sources.

Plagiarism of any kind will not be tolerated. In general terms, plagiarism is the act of representing someone else's words or ideas as one's own without crediting the true source or origin.

6.2. Review and Clearance Policy

ORS laboratory management, quality managers, and analysts shall follow current FDA and local policy and procedures for review and clearance of scientific articles. Scientific articles can include, but not limited to the following: publications, articles, speeches, presentations and Laboratory Information

Bulletins (LIB). ORS Labs must follow Agency wide publication clearance practices outlined in Staff Manual Guide (SMG) 2126.3. All potential publications must be reviewed and cleared through local laboratory management (and quality personnel, if appropriate), with final local concurrence provided by the Laboratory Director. The locally approved publication is then submitted to ORS/ORCET via the automated manuscript submission portal for review by appropriate subject matter exerts (SME). If changes regarding technical or policy aspects are warranted, ORCET will return the publication with comments. If no changes are necessary or comments have been satisfactorily addressed, clearance will be provided by ORCET and author/local management will be notified.

Clearance for oral presentations are to be submitted, reviewed, and cleared using the Appearance Request Tracking System (ARTS).
Appearance Request Tracking System (ARTS)

FDA has a policy stating that scientific articles are reviewed for the following: scientific and technical accuracy; agreement with current Agency policy or future regulatory programs; and not adversely affecting the requirements of policies on other FDA centers or offices.

It is the responsibility of the author to make revisions and corrections deemed necessary by their supervisors, quality manager, laboratory director and ORS reviewer during the clearance process.

A disclaimer should be added to the scientific article. Generic disclaimers can be obtained from ORCET.

6.3. Authorship

Authorship refers to the listing of participating scientists' names in all communications, oral and written, experimental results and their interpretation to scientific colleagues.

Authorship is based on significant contributions to the conceptualization, design, execution or interpretation of a research study.

For those individuals who have limited contributions to a study, e.g. providing certain advice, reagents, analyses and support, these individuals may more appropriately be acknowledged but not listed as co-authors. HHS Office of Research Integrity Author Guidance

Any authorship disputes need to follow the established agency guidelines and referred to the appropriate agency level committees for resolution.

7. References

1. ORA Laboratory Manual, Volume II, ORA-LAB.5.4.5, Methods, Method Verification and Validation
2. FDA Office of Foods and Veterinary Medicine, Guidelines for the Validation of Chemical Methods for the FDA FVM Program, 3rd Edition, October 2019. (available on FDA.GOV at Foods Program Methods Validation Processes and Guidelines)
3. FDA Office of Foods and Veterinary Medicine, Guidelines for the Validation and Analytical Methods for the Detection of Microbial Pathogens in Foods and Feeds, 3rd Edition, October 2019. (available on FDA.GOV at Foods Program Methods Validation Processes and Guidelines)
4. Guidelines for the Validation of Analytical Methods for Nucleic Acid Sequence-Based Analysis of Food, Feed, Cosmetics and Veterinary Products, 1ST Edition, September, 2019 (available on FDA.GOV at Foods Program Methods Validation Processes and Guidelines)
5. FDA Office of Foods and Veterinary Medicine, Acceptance Criteria for Confirmation of Identity of Chemical Residues using Exact Mass Data for the FDA Foods and Veterinary Medicine Program, 1st Edition, September 2015. (available on FDA.GOV at Foods Program Methods Validation Processes and Guidelines)
6. ORA-LAB.014, Component Automated Research Tracking System
7. ORS.005, Laboratory Information Bulletin
8. ORA Laboratory Manual, Volume II, ORA-LAB.4.13, Records and Data Management
9. FDA Policy on the Review and Clearance of Articles to be Published in Scientific or Professional Journals (Link to FDA Policy on The Review And Clearance Of Articles To Be Published In Scientific Or Professional Journals)
10. U.S. Department of Health and Human Services, PHS, Guidelines for the Conduct of Research within the Public Health Service, January 1, 1992
11. FDA Staff Manual Guide Volume IV, 2126.3
12. FDA Staff Manual Guide Volume III, 2126.4
13. FDA Staff Manual Guide Volume IV, 9003.1
14. FDA Staff Manual Guide Volume IV, 9010.1

8. Document History

Revision #	Status* (D, I, R)	Date	Author Name and Title	Approving Official Name and Title
1.2	R	06/23/05	LMEB	LMEB
2.0	R	12/06/06	LMEB	LMEB
2.1	R	06/06/08	LMEB	LMEB
2.2	R	08/15/08	LMEB	LMEB
2.3	R	12/03/08	LMEB	LMEB
2.4	R	07/13/11	LMEB	LMEB
2.5	R	02/06/12	LMEB	LMEB
2.6	R	01/31/13	LMEB	LMEB
03	R	05/05/2020	LMEB	LMEB

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

9. Change History

Revision #	Change
2.0	Chapter underwent major revision to reflect the current Method Development and Validation Program.
2.1	6.5.2.2 and 6.5.2.3 – Calls for Proposals changed from quarterly to semiannually. Reference 2. changed to the accessible policy on publication.
2.2	Table of Contents – 6.5.2.1-6.5.2.7 revised Appendix III – added – added “the Centers” to second paragraph 6.5.2.1- 6.5.2.7 - revised 6.5.2.6 – revised sixth paragraph
2.3	6.3.2 – inserted “in” after described 6.5.1. Technology Exploration – changed implemented to accepted 6.5.2.3 – added (Appendix III) at end of first paragraph 6.5.2.4 – updated SOP information in fourth paragraph 6.5.2.5 Scientific Articles – added last paragraph
2.4	6.5.2.2 1. a., third bullet – changed “or” to “and” Appendix I – replaced Appendix III – replaced
2.5	6.1 – added FDA Office of Foods Guidelines for Validation in Food to fourth sentence 6.2 – deleted “of this program”; added and/or in conjunction with the Office of Foods to third sentence 6.3 – deleted first sentence 6.3.2 – deleted “Sources” from the title and deleted sentence 6.4 – changed Associate Commissioner for Regulatory Affairs to Office of Regulatory Affairs Associate Commissioner 6.5.2 – added NOTE: and revised section for CARTS implementation 6.5.2.1 – changed “semiannually” to “at least annually” in second paragraph 6.52.4 – added last two sentence to first paragraph
2.6	Header - Division of Field Science and DFS changed to Office of Regulatory Science and ORS throughout the document 6.5.2.6 – RPN Project ######## changed to CARTS Project ########
03	Updated procedure to include ORCET. Removed Appendices I (Method Development and Validation Project Record) and III (MDVP Flowchart). Removed Attachment for LIB format The document was reformatted and as a result, section and bullet numbering changed. Removed instructions for CARTS submissions Removed instructions for FACTS reporting of hours Updated the References to include additional entries from the Staff Manual Guide Removed footnotes for References Updated links for the ARTS homepage Added link for the HHS Authorship Guide

10. Attachments

None