LABORATORY QUALITY MANUAL

Third Edition

Implemented and Effective: October 2009

Note:

The CFSAN Laboratory Quality Manual contains basic quality requirements. The Quality Management System is in the process of being implemented; therefore, some procedures are in draft form. As implementation takes place, more supporting documents may be added.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
College Park, Maryland 20740

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: OCT 3 0 2000

From: Acting Deputy Director for Operations, CFSAN (HFS-3)

Subject: CFSAN Laboratory Quality Manual, Third Edition - Release

To: Management Council, Deputy/Associate Office Directors

The Center for Food Safety and Applied Nutrition (CFSAN) Quality Assurance Team is charged with revising the Laboratory Quality Manual (LQM), third edition for the CFSAN. The purpose of the LQM is to provide Center staff with the fundamental information to implement basic quality concepts, principles and practices throughout CFSAN laboratories.

Additionally, this manual serves as a key element in the implementation of a Quality Management System. The targeted audience for this manual includes Center Laboratory Supervisors (Office Directors, Division Directors, Branch Chiefs, Team Leaders and other supervisors, including Acting Supervisors), laboratory researchers, and other key laboratory personnel.

I encourage all Center research staff to utilize this manual for guidance in their research and routine laboratory activities.

Laura M. Tarantino, Ph.D.

cc:
HFS-003, Watson
HFS-006, Wirtz
HFS-657, Zelinsky

FDA - Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
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FDA CFSAN Quality Assurance Team Transmittal Notice

Laboratory Quality Manual

Transmittal: QAT-2008-2
Date: October 30, 2009

Subject: Center for Food Safety and Applied Nutrition (CFSAN) Implementation of the Laboratory Quality Manual (LQM) third edition.

Target Audience: CFSAN Laboratory Supervisors (Office Directors, Division Directors, Branch Chiefs, Team Leaders and other supervisors, including Acting Supervisors), Laboratory Staff, and other key laboratory personnel.

Background: This document serves as notification of the Center for Food Safety and Applied Nutrition's (CFSAN) implementation of the Laboratory Quality Manual (LQM) third edition. The LQM establishes the policies and instructions related to laboratory quality assurance in CFSAN. In addition to complying with FDA Staff Manual Guide 2020, *Quality System Framework for Internal Activities*, the manual provides a central resource for understanding CFSAN's quality system and provides guidance on quality concepts, principles, and practices.

A draft copy of the manual was originally released in May 2008 for review and comments to be provided by February 2009. CFSAN Laboratory Operations Work Group members from March 2009 through May 2009 conducted an additional review of the LQM. Training on the LQM was conducted in September 2008 and mock assessments were performed on select research laboratories from July 2008 through July 2009. The LQM has been reviewed extensively by all stakeholders and interested parties.

Actions Required: The LQM is effective 30 October 2009. All CFSAN Laboratory staff should utilize the final document as a guidance document. All CFSAN laboratory staff should familiarize themselves with the LQM. All comments, inquires, and questions regarding the LQM should be forwarded to the Quality Assurance Team Leader.

Availability: An on-line version of the LQM will be maintained as the current document. To view this document, CFSAN laboratory staff may access the QA CFSAN website via the CFSAN intranet:
http://inside.fda.gov:9003/downloads/CFSAN/OfficeoftheCenterDirector/LaboratoryQualityAssurance/UCM171045.pdf

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FDA CFSAN Quality Assurance Team Transmittal Notice

For questions about this transmittal, contact: CFSAN Quality Assurance Team via QACFSAN@fda.hhs.gov

Issued by authority of: Denise Riley, Senior Management Advisor HFS-003

Transmittal Distribution:
TO: CFSAN-CPK1-LAB, CFSAN-CPK2-LAB, CFSAN-MOFF-LAB, CFSAN-DI-LAB and CFSAN-MOD1-LAB
CC: CFSAN QA Team

Center for Food Safety and Applied Nutrition
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College Park, Maryland 20740

Summary of Changes

CFSAN Laboratory Quality Manual, 3rd Edition

Date: October 30, 2009

Subject: Summary of changes for the Draft Laboratory Quality Manual (LQM) to the Final LQM.

Target Audience: Laboratory Supervisors (Office Directors, Division Directors, Branch Chiefs, Team Leaders and other supervisors, including Acting Supervisors), Laboratory Staff, and other key laboratory personnel.

Background: This document serves as notification of the summary of changes to the draft Laboratory Quality Manual (LQM) third edition. The draft copy of the LQM was originally released to the Center for Food Safety and Applied Nutrition (CFSAN) in May 2008 for review and comments. CFSAN Laboratory Operations Work Group members conducted an additional review of the LQM during a 3 month period. This document communicates the summary of changes received during the entire 12 month review period.

List of Changes: The following is a summary of the changes.

1. Updated all references to any links due to the implementation of the Web Content Management System (WCMS).
2. Removed all references indicating that the LQM is a draft document.
3. Updated some formatting changes.
4. Pages 35 - 38, Documents and Records – Information was updated to comply with the new Agency guidance for documents and records.

Actions Required: Laboratory Supervisors (Office Directors, Division Directors, Branch Chiefs, Team Leaders and other supervisors, including Acting Supervisors), Laboratory Staff, and other key laboratory personnel are encouraged to review the summary of changes with their staff members, update Quality Control Plans as needed and implement any procedures required to be in compliance.

Availability: An on-line version of this document will be maintained with the final version of the LQM. To view this document, CFSAN laboratory staff may access the QA CFSAN website via the CFSAN intranet:
http://inside.fda.gov:9003/downloads/CFSAN/OfficeoftheCenterDirector/LaboratoryQualityAssurance/UCM171045.pdf

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Summary of Changes

CFSAN Laboratory Quality Manual, 3rd Edition

For questions about this transmittal, contact: CFSAN Quality Assurance Team via QACFSAN@fda.hhs.gov

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CC: CFSAN QA Team

Foreword

The use of a quality systems approach is increasing within the Food and Drug Administration (FDA). To help enhance consistency, efficiency and effectiveness of day-to-day work, the FDA has adopted a quality system model and established an FDA-level committee to help employ this quality system initiative.

The Center for Food Safety and Applied Nutrition (CFSAN) Quality System (QS) provides guidance to: (1) design and develop processes, products, and services related to CFSAN's mission, the FDA's regulatory mission, and to critical management and administrative support services, and (2) continually improve and strengthen product and service quality.

This Laboratory Quality Manual contains the required information to implement quality principles and practices throughout CFSAN's laboratories. This manual serves as a key element in the implementation of a Quality Management System (QMS). The anticipated audience for this manual includes those in the public, regulated industry, counterpart agencies, CFSAN scientists and other FDA staff members who wish to understand CFSAN QMS.

Training is an essential element of QS implementation. For CFSAN, training is necessary prior to achieving accountability for the policies and procedures described in this manual. For others, general information about quality systems may be found on the Internet at:

- American Society for Quality, "Learn About Quality" (www.asq.org)

Final Release Note

The CFSAN QMS is not fully implemented. Accordingly, some implementing procedures are in draft stage. Under the supporting information headings, these are marked as 'draft.' As implementation progresses and procedures are finalized, the supporting information references will be updated.

Initially released: 2008

Final Implemented and Effective: October 2009

Distribution within the FDA: FDA employees may access the current ('controlled') version of the CFSAN Laboratory Quality Manual through the CFSAN Intranet website - under Laboratory Quality Assurance Program.

Public distribution: The public may obtain a copy of the CFSAN Laboratory Quality Manual by making a written Freedom of Information request (www.fda.gov, see "Freedom of Information").

Comments: CFSAN welcomes comments as to how this publication may be improved. Please send your comments to the Quality Assurance email box at QACFSAN@fda.hhs.gov

Document History				
VERSION #	STATUS (I,R,C) I-Initial, R-Revised, C-	DATE APPROVED	LABORATORY QUALITY MANUAL	
			CONTACT	APPROVING OFFICIAL
4.0	Revised		CFSAN Laboratory QA Team (HFS-003)	

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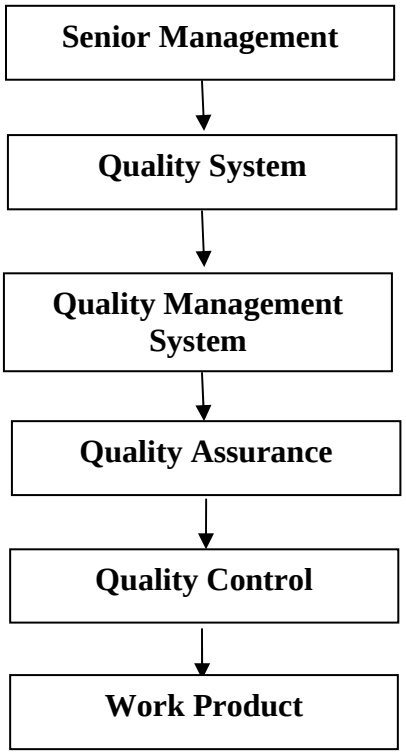
A. CFSAN Organizational Chart

1.0 INTRODUCTION

1.1 Quality Statement

The Center for Food Safety and Applied Nutrition (CFSAN) Quality System (QS) provides guidance on (1) designing and developing processes, products, and services related to CFSAN's mission, FDA's regulatory mission, and to critical management and administrative support services, and (2) continually improving and strengthening product and service quality. This will be done by implementing interrelated elements, including the Quality Management System (QMS), the quality assurance (QA) program, the quality control (QC) program, as well as additional policies and procedures. The Laboratory Quality Manual (LQM) is a key component for understanding the organization's quality system and is meant to provide clear organizational guidance. It is incumbent upon CFSAN personnel to have an effective working knowledge of, and participate in, CFSAN's Quality System and its components.

In designing and implementing a quality system, an organization determines the following: (1) the customers' stated and implied needs; (2) applicable regulatory requirements for work processes and products; (3) other requirements identified by the organization or other government agencies. In this respect, CFSAN QS practices are being designed to be in alignment with FDA Staff Manual Guide (SMG) 2020, *Quality System Framework for Internal Activities*. Several elements of CFSAN's Quality Framework are depicted below.



1.2 Scope and Objectives (LQM)

Scope
The scope of the Laboratory Quality Manual (LQM) includes all research and analytical testing performed throughout CFSAN.

Objectives
This manual establishes the policies and instructions related to laboratory quality assurance in CFSAN. A main objective is to provide a central resource for understanding the organization's quality system and to provide clear guidance when producing work products within CFSAN. Another objective is to provide direction and guidance to CFSAN staff regarding quality principles and practices, internal audits, corrective/preventive action plans, and continual improvement activities.

1.3 Background

The FDA is a government agency within the Department of Health and Human Services (DHHS). The FDA promulgates and/or enforces applicable Federal regulations in titles 21, 29, 40, and 49 of the Code of Federal Regulations. These regulations are issued under the authority of the Federal Food, Drug, and Cosmetic Act; the Public Health Service Act; and other laws. In order to fulfill its regulatory mission, FDA must ensure that its laboratory work products are of appropriate level of quality and reliability.

CFSAN laboratories operate permanent facilities in five locations across the United States. Those locations are:

- 8301 Murkirk Road, Laurel, Maryland (MOD 1)
- 5100 Paint Branch Parkway, College Park, Maryland (Wiley Building)
- 4300 River Rd., College Park, Maryland (University Station)
- 6502 South Archer Rd, Summit-Argo, Illinois (Moffett Center)
- 1 Iberville Dr., Dauphin Island, Alabama (Dauphin Island)

In 1981, a Quality Assurance Task Force and Oversight Committee was formed and recommendations to the Director of the Bureau of Foods (CFSAN predecessor organization) were made with regard to the conduct of laboratory work. This was accomplished by the Task Force in two phases. Phase I entailed an extensive review of the conduct of GLP studies, which the Commissioner directed must be conducted in full accordance with a regulation governing such nonclinical (GLP) studies – namely, 21 CFR part 58. Phase II addressed the development of a quality control program for the remaining laboratory work.

The Director of the Bureau of Foods acted on these recommendations and the revised Quality Assurance (QA) Program became operational in 1981. From 1981 to 1995, the original Laboratory QA Manual was the basis for the QA Program. In 1992, CFSAN had a major reorganization that affected the structure and operations of laboratory personnel and facilities. The Laboratory Quality Manual (LQM) 2nd Edition was issued in 1995. This manual defined and described CFSAN's updated QA program. The 1995 version of the LQM is superseded by this 3rd edition. The 2007/2008 reorganization within CFSAN and recent changes in quality practices and principles have contributed to the need for this revision.

1.4 Special Considerations

CFSAN has two laboratory facilities located outside of the Washington metropolitan area, both of which are committed to producing quality work products. Both facilities conduct research in compliance with applicable requirements outlined in this manual. It is acceptable however, for each of the two facilities to develop and operate under local quality control plans that are in alignment with the elements outlined in this manual.

Dauphin Island
Dauphin Island is a CFSAN facility located in Dauphin Island, Alabama. The facility operates under the Office of Food Safety (OFS), Division of Seafood Science and Technology (DSST). DSST scientists conduct multi-disciplinary research that supports the public health and regulatory mission of the FDA. DSST research relates primarily to the safety and wholesomeness of seafood and the impact and interaction of environmental factors on these qualities. Emphasis is on methods development, risk characterization, and intervention strategies as they relate to microbial pathogens, marine biotoxins and aquaculture drugs. Additional information regarding Dauphin Island, Microbiological Hazards Science Branch (MHSB) and Chemical Hazards Science Branch (CHSB) can be located in the Staff Manual Guide (http://inside.fda.gov:9003/PolicyProcedures/StaffManualGuide/VolumeIOrganizationsandFunctions/ucm051840.html).

The DSST Laboratory Quality Control (LQC) Plan is intended to substantiate the validity of the data produced by their laboratories. The procedures established by the laboratory are designed to reduce or eliminate errors caused by investigators, supplies, equipment, or methods. The implementation of the plan should yield high quality data and produce results of high integrity. Acceptance and implementation of the plan by all laboratory personnel is required for the LQC program to be effective. The LQC Plan components include documentation, best practices (includes project reports, project plan development, and monitoring), materials, instruments and equipment, and environment.

The Moffett Center
The Moffett Center is a CFSAN facility located in Summit-Argo, Illinois. The facility operates under the Office of Food Safety (OFS) to support research and regulatory activities in accordance with the public health mission of the FDA. The Division of Food Processing Science and Technology (DFPST) conducts multi-disciplinary research in areas of food technology and food process engineering and are involved in cooperative projects associated with the National Center for Food Safety and Technology (NCFST). The Food Technology Branch (FTB) and Process Engineering Branch (PEB) comprise the primary research components of the DFPST.

The Moffett Center's Laboratory Proficiency and Evaluation Team (LPET), carries out a congressionally mandated regulatory support program under the Grade A Pasteurized Milk Ordinance and a Memorandum of Understanding (Compliance Program 7018.003) with the National Conference of Interstate Milk Shippers. Under this program, the State and Territorial Central Milk laboratories and the analysts are accredited or certified by the LPET . As a part of the certification program, the LPET conducts proficiency testing programs for milk. In addition, the LPET is authorized by an intra-agency agreement to conduct *"Microbiological Methods and Programs"* (Project Number 22979; FDA Compliance Program 7318.004), which is a microbiological proficiency testing program for Shellfish Testing Laboratories (State, Local government, and Private) and Food Laboratories.

1.5 Definitions

Acclimate: To adapt to a new environment.

Audit: A methodical, formal, systematic, examination and review of a process or product conducted by qualified persons, other than those responsible for the conduct or preparation of the process or product.

Batch: A specific quantity or lot of a test or control article that has been characterized according to 21 CFR § 58.105(a).

Best practices: Techniques, methods, processes, and activities that are recognized within the scientific community as delivering appropriate quality, excellence, or results.

Continual improvement: Ongoing activities to evaluate and positively change products, processes, and the quality system to increase effectiveness (SMG 2020).

Control article: Any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any article other than a test article, feed, or water that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article.

Corrective action: Reactive activity to prevent recurrence of a detected nonconformance (SMG 2020). Action taken to eliminate or prevent a recurrence of root cause(s) and symptoms(s) of an existing deviation or nonconformance with respect to CFSAN laboratory policies or procedures and/or applicable regulations.

Critical Control Point (Area): A point, step, or procedure in a process at which controls can be applied, and a deviation can, therefore, be prevented, eliminated, or reduced to acceptable levels.

Customer: In this document customer is defined as: A person having an immediate, secondary, or other interest in a product or service that an organization provides.

Deviation: A nonconformance or departure of a characteristic from a specified product, process, or system requirement.

Element: A constituent part; a distinct section or portion within a larger group; one of the factors determining the outcome of a process.

Equipment: All instruments, measuring devices, and computer systems used in evaluating and or performing research.

Finding: A conclusion of relative importance based on observation(s) and/or research.

Good Clinical Practice: A set of rules and regulations provided by the International Conference on Harmonization (ICH), an international body that regulates clinical trials involving human subjects. Good clinical practice guidelines include protection of the rights of humans who are used as subjects in clinical trials. It also provides assurance of the safety and efficacy of the newly developed compounds.

Good Laboratory Practice (GLP): A system of controls for laboratories and research organizations, which ensure the consistency and reliability of results e.g., 21 CFR part 58 as well as GLP OECD Principles and Guidance for Compliance Monitoring. A study conducted in compliance with GLP is also commonly referred to as a nonclinical laboratory study. The nature of the research as well as the intent of the study determines whether the study is considered GLP or not.

Inspection: Measuring, examining, testing, and gauging one or more characteristics of a product or service and comparing the results with specified requirements to determine whether conformity is achieved for each characteristic.

Internal audit: An audit conducted within an organization by members of the organization to measure the strengths and weaknesses against its own procedures and/or external standards. It is also known as a first party audit.

Investigation: To observe or study by close examination and systematic inquiry, to make a systematic examination, to conduct an official inquiry. Investigations may be triggered by multiple factors, including but not limited to, systemic errors, official inquiry, and multiple nonconforming inspections.

Lifecycle: The activities that plan, produce, deliver, and service a work product (SMG 2020).

Management review: Formal evaluation by top management of the status and adequacy of the quality system in relation to quality policy and objectives.

Master schedule sheet: A list of all nonclinical laboratory studies conducted at the testing facility indexed by test article and containing the test system, nature of study, date the study was initiated, current status of each study, identity of the sponsor, and name of the study director.

Metric: The measure used to evaluate the quality of a process or product/service.

Monitor: In this document monitoring means: To watch over; check systematically for the purposes of collecting metrics (SMG 2020).

Nonclinical laboratory study (GLP): *In vitro* or *in vivo* experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility or to determine physical or chemical characteristics of a test article.

Nonconformance: An unfulfilled requirement; "nonconformity" is an equivalent term (SMG 2020).

non-GLP study: A study that involves laboratory experiments that are not intended to fall under the scope of 21 CFR part 58 or GLP OECD Principles and Guidance for Compliance Monitoring.

Peer assessment: One of the primary mechanisms for assuring quality in science.

Preventive action: Action to eliminate the cause of a potential nonconformity or otherwise undesirable situation.

Principal Investigator: In this document principal investigator is equivalent to a project lead in CFSAN; an individual who has primary responsibility for performing or overseeing research.

Procedure: Specified way to perform an activity. A procedure typically produces a specific result, either in the form of a measurement result or an end product.

Process: A set of interrelated activities (tasks, procedures, sub-processes) that transform inputs into desired outputs (SMG 2020).

Process based audit: An audit that assesses the steps or activities involved in completing or executing a specific task or a group of related tasks.

Protocol: In the natural sciences, a protocol is a predefined written procedural method in the design and implementation of experiments. This should establish standards that can be adequately assessed by peer review and provide for successful replication of results by others in the field. It should include safety,

procedural, equipment, and reporting standards. A major part of this protocol is predefining and documenting excluded data to avoid bias.

Quality: A measure of a product's or service's ability to satisfy the customer's stated or implied needs (SMG 2020).

Quality Assurance: Proactive and retrospective activities that provide confidence that requirements are fulfilled (SMG 2020). All of the planned and systematic actions used in a Quality System to provide adequate confidence that a product, service, or process will satisfy given requirements for quality.

Quality Assurance Unit (Team): A person or organizational element, except the study director, designated by testing facility management to perform the duties related to quality assurance, including monitoring each GLP study to ensure management that the quality elements (e.g., facilities, equipment, personnel) are in conformance with applicable standards.

Quality control: The operations, techniques, and activities of a quality system that are used to fulfill requirements for quality of product, service or process.

Quality control plan: Document specifying which procedures and associated resources shall be applied by whom and when to a specific project, product, process or contract.

Quality element: A component of the quality system.

Quality indicator: An element of a quality monitoring process that can be identified as needing improvement.

Quality management system: Accountibility for all activities and functions that determine the quality policy, objectives, and responsibilities, and ensure that such activities are implemented. Quality planning, quality assurance, quality control, and quality improvement are components of a quality system.

Quality planning: The processes that specify quality standards, practices, resources, specifications, and the sequences of activities relevant to particular products, services, projects, or contracts.

Quality policy: The intentions and directions of an organization regarding quality that are established by FDA and CFSAN management.

Quality system: A quality system (QS) is a formalized business practice that defines management responsibilities for organizational structure, processes, procedures and resources needed to fulfill product/service requirements, customer satisfaction, and continual improvement.

Quarantine: Enforced isolation, typically to contain the spread of something considered dangerous.

Raw data: According to Federal GLP regulations, laboratory worksheets, records, memoranda, notes, or exact copies thereof, that are the result of original observations and activities of a laboratory study and are necessary for the reconstruction and evaluation of the report of that study. In the event that exact transcripts of raw data have been prepared (e.g., tapes which have been transcribed verbatim, dated, and verified accurate by signature), the copy of that transcript may be substituted for the original source as raw data. Raw data may include photographs, microfilm or microfiche copies, computer printouts, magnetic media including dictated observations, and recorded data from automated instruments. Interpretation of what constitutes "raw data" for non-GLP studies is less rigorous than the definition found in 21 CFR part 58.

Regulatory Sample: Compliance samples, official or investigational factory samples, official or investigational surveillance samples, official or investigational complaint samples, official or investigational documentary samples, and official post-seizure samples.

Self-evaluation: Assessment by supervisors and staff members of their own performance with respect to analytical methods, discipline-specific activities, statistics, control charting, standardization activities, QA, sampling, calibration, data evaluation, and skill in reporting and report writing.

Specimen: Any material derived from a test system for examination or analysis.

Sponsor: With respect to 21 CFR 58, the person who initiates and supports, by provision of financial or other resources, a nonclinical laboratory study.

Stakeholder: In this document stakeholder means: An individual or organization having ownership or interest in the delivery, results and metrics of the quality system framework or business process improvements (SMG 2020). Typical stakeholders are customers, employees, stockholders, board of directors, and executives.

Standard Operating Procedure (SOP): Written instruction designed to achieve uniformity of the performance of a specific function. SOPs set forth a routine or standardized laboratory function.

Study completion date: With respect to 21 CFR 58, the date the final report is signed by the study director.

Study director: With respect to 21 CFR 58, the individual responsible for the overall conduct of a nonclinical laboratory study (21 CFR 58). A scientist or other professional of appropriate education, training, and experience, or combination thereof, who possesses overall responsibility for the technical conduct of the study, as well as interpretation, analysis, documentation, and reporting of results of the study, and represents the single point of study control.

Study initiation date: With respect to 21 CFR 58, the date the protocol is signed by the study director.

Supporting information: Within this Quality Manual, this term designates other directives used to implement the requirement being discussed. If marked DRAFT, the directive is planned but not yet available.

Test article: With respect to 21 CFR 58, a food additive, color additive, drug, biological product, electronic product, medical device for human use, or any other article subject to regulation under the Federal Food, Drug, and Cosmetic Act or under sections 351 and 354-360 of the Public Health Service Act (PHSA).

Test system: With respect to 21 CFR 58, an animal, plant, microorganism, or subparts thereof to which the test or control article is administered or added for study. Test system also includes appropriate groups or components of the system not treated with the test or control articles.

Testing facility: With respect to 21 CFR 58, a person who actually conducts a nonclinical laboratory study, i.e., actually uses the test article in a test system. Testing facility includes any establishment required to register under section 510 of the Federal Food, Drug, and Cosmetic Act that conducts nonclinical laboratory studies and any consulting laboratory described in section 704 of the Federal Food, Drug, and Cosmetic Act that conducts such studies. Testing facility encompasses only those operational units that are being or have been used to conduct nonclinical laboratory studies.

Work product: Encompasses the products and services that CFSAN provides to internal and external customers, e.g., analyses and worksheets; report drafting and publications.

Acronyms

AAALAC	Association for the Assessment and Accreditation of Laboratory Animal Care, International
AWA	Animal Welfare Act
CAPA	Corrective Action Preventive Action
CFSAN	Center for Food Safety and Applied Nutrition
CARTS	CFSAN Automated Research Tracking System
CHSB	Chemical Hazards Science Branch
CP	Compliance Program
DHHS	Department of Health and Human Services
DFPST	Division of Food Processing Science and Technology
DSST	Division of Seafood Science and Technology
FDA	Food and Drug Administration
FTB	Food Technology Branch
GLP	Good Laboratory Practice
IACUC	Institutional Animal Care and Use Committee
ICH	International Conference on Harmonization
LPET	Laboratory Proficiency and Evaluation Team
LQA	Laboratory Quality Assurance
LQM	Laboratory Quality Manual
MSDS	Material Safety Data Sheets
MHSB	Microbiological Hazards Science Branch
NCFST	National Center for Food Safety and Technology
NIST	National Institute of Standards and Technology
OECD	Organization for Economic Co-operation and Development
OFS	Office of Food Safety
OLAW	Office of Laboratory Animal Welfare
ORA	Office of Regulatory Affairs
PEB	Process Engineering Branch
PHSA	Public Health Service Act
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
QS	Quality System
SM	Senior Manager
SMG	Staff Manual Guide
SOP	Standard Operating Procedure

2.0 QUALITY SYSTEMS OVERVIEW

CFSAN, a component of the FDA, is recognized as a leader in food and cosmetic safety, food defense, improving nutrition, and improving dietary supplement safety. The research performed in CFSAN's laboratories contributes greatly to the FDA's mission, which includes continual process improvement. It is important that work conducted by and for CFSAN be of an appropriate level of quality, be fully documented, and be reproducible. Accordingly, in concert with SMG 2020 and other source guidance documents, CFSAN is implementing a Quality System (QS) that provides guidance, policies, and procedures to ensure accountability and credibility of work products and processes. The above will be achieved through implementation of the LQM, internal audits, and development of pertinent operating procedures.

Quality systems take on various maturity levels. In contradistinction to quality-oriented research processes in-house, the relative maturity of quality systems (e.g., product/service/operations processes) in organizations in general may be characterized as dysfunctional, awakening, developing, maturing, or world-class (*The Certified Manager of Quality/Organizational Excellence Handbook,* 2005 Russell Westcott). A world class QS is one that has been implemented and nurtured over time. Matching priorities with adequate resources serve to underscore management's commitment to quality in the workplace. CFSAN's QS is in the early stages of this maturation process and will continue to strive for world-class status. To further this process, a partnership will be developed with CFSAN staff (and their customers/stakeholders) performing and/or supervising laboratory studies. Adherence to a system predicated on developing and following proper procedures is critical.

Supporting information that will assist in fulfilling these requirements:

- Quality System Framework Document
(*http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm052570.htm*)
- Quality System Scope document
(*http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm052571.htm*)

2.1 Quality Management System

A quality management system emphasizes accountability for all activities and functions that determine the quality policy, objectives, and responsibilities, and ensure that such activities are implemented. Quality planning, quality assurance, quality control, and quality improvement are components of a quality system.

A key element of a QMS is to identify Customers/Stakeholders and their requirements
Stakeholders include all those parties with an interest in FDA work products or service. Customers are a subset of stakeholders and receive the work product or service and may appropriately determine the needs and requirements associated with that work product or service. According to FDA SMG 2020:
Customer is an internal or external recipient of a product or service anywhere along the product's life-cycle.

Examples:
Laboratories or organizations that send 'regulatory sample' to CFSAN for testing (external customer).
A fellow researcher who uses your research findings for future studies (internal customer).

Stakeholder is an owner or interested party regarding the delivery of a product or service.
Examples:
A senior manager (SM) who is interested in using the results of your study for a given reason. The stakeholder could be the SM and others depending on the type of research you are performing.
A scientist who uses a select agent in their research. The stakeholders could be the Office Director, SM, and Safety office, as well as others.

There is no hard and fast distinction between customers and stakeholders (see Section 1.5, Definitions).

Customers identified can include, but are not limited to:
Fellow scientists (internal customers)
The public — nationally and internationally (external customers)

Stakeholders identified within CFSAN can include, but are not limited to:

- Senior management
- Office directors
- Quality assurance unit or team
- Laboratory supervisors
- Records management
- Researchers
- Institutional Animal Care and Use Committee (IACUC)
- Safety Office

2.2 Scope and Objectives

CFSAN's QMS applies to activities that significantly affect the quality of CFSAN work processes and the resulting work products and services. CFSAN's QMS includes the following elements:

a) The QMS applies to all CFSAN laboratories, including the Moffett Center and Dauphin Island.
b) The QMS applies to all facilities—permanent, mobile, or temporary—where CFSAN work activities take place.
c) The QMS defines the responsibilities and authorities for CFSAN activities that significantly affect work product quality.
d) The QMS includes policies, procedures, quality requirements, forms, references, and records of research activities.
e) The QMS incorporates a review mechanism.

A main objective of a QMS is to maintain an effective, documented quality system to ensure quality is incorporated into work products and services. This is accomplished through the implementation of work processes and guidelines outlined in part in this manual.
Other objectives of a QMS are to:

1. Provide clear logical explanations of the quality elements.
2. Oversee CFSAN's quality activities through internal audits, corrective/preventive action plans, and continual improvement activities.
3. Develop quality metrics used to keep management informed of the activities performed CFSAN-wide.

Overview

Within the QS, a QMS manages the quality of work in CFSAN. Appropriate work quality is critical to the products and services that CFSAN provides to customers and stakeholders. The majority of CFSAN's laboratory work products are results derived from research studies and method development, and CFSAN's QMS must ensure that the results of the work products are reproducible, accurate and of good quality.

To build quality into the organization, CFSAN plans, implements, documents, and assesses work activities to facilitate continual improvement. CFSAN's goals are to ensure work products, services, and decisions are fit for their intended uses, and that resources and processes are aligned with CFSAN's strategic priorities. In this regard, the QMS shall be designed to meet: (1) the customers' and stakeholders' stated and implied needs, (2) applicable regulatory requirements, and (3) other requirements identified by the organization, the FDA, or other government agencies.

The CFSAN Quality Manual meets the requirements of FDA SMG 2020, *Quality System Framework for Internal Activities*. The Quality Manual provides the scope and structure of the CFSAN laboratory QMS—the policies, objectives, authority, accountability, and plans needed to ensure quality in work processes, products and services. A quality system is necessary to control, ensure, and improve the effectiveness of the processes used to deliver a quality product or service. Implementation of a Quality System is of benefit to organizations and their employees for the following reasons:

1. It enhances the credibility and accuracy of work products.
2. It decreases the cost, time, and labor resources associated with repeating inaccurate work product results ("do it right the first time").
3. It frees up time for staff to perform other activities because the task was performed correctly the first time.
4. It ensures consistency and control when executing specific tasks.

Applicable Requirements

FDA has instituted agency-wide requirements for quality systems (SMG 2020).

In designing and implementing a quality system, the organization determines the regulatory requirements for its work processes and products and adopts quality system requirements from relevant standards. The standards that CFSAN has chosen to comply with are:

- As a component of a Federal agency, CFSAN is subject to statutes, regulations, and orders that are incorporated into the QMS. Federal and FDA-wide policies and procedures supersede CFSAN policies and procedures.

- Statutes and regulations that direct FDA activities may set requirements for QMS procedures (e.g., OMB circular A-123) that affect management's responsibility for internal controls.

    - CFSAN is not seeking registration to any third-party standard, although CFSAN laboratories may achieve and maintain third-party accreditations, e.g., QA Program for dietary supplement analyst proficiency-National Institute of Standards and Technology (NIST). Some elements of the CFSAN QMS are adapted from an international standards organization for quality systems and for analytical proficiency.

    - Continual improvement of the CFSAN QMS may be based on quality system and work standards, e.g., ANSI/ASQ Z1.13-1999: *Quality Systems Guide for Research,* published by the American Society of Quality.

- Good Laboratory Practice (GLP) requirements are mainly based on 21 CFR 58.

Supporting information that will assist in fulfilling these requirements is:

- www.FDA.gov
- FDA Staff Manual Guides, e.g. FDA SMG 2020, *Quality System Framework for Internal Activities*
- Information Quality Act

Documentation

Organizations use directives and evidentiary records to establish and maintain a quality system and to support effective and efficient work processes. Customer, stakeholder, and regulatory needs drive the type and degree of system and work documentation. Various directives, standards, statutes, regulations are all examples of applicable requirements.

1) The CFSAN QMS is defined by:

Type	Description
1. Laboratory Quality Manual	The Quality Manual contains quality policies for FDA's CFSAN laboratories.
2. National Directives	Nationally mandated directives, which are used FDA-wide or CFSAN-wide, including: • Quality system procedures, instructions and forms; • Work directives • Staff Manual Guides

3. Local Directives	Local directives include quality system and work procedures and instructions for a specific unit. Generally referred to as standard operating procedures (SOPs), they may be responsive to national directives.
4. Records	Includes work and quality records and many CFSAN in-process and final documents.

2) CFSAN centrally maintains general internal SOPs via the CFSAN intranet. These documents are a mixture of procedural and instructional information.

Management Responsibility

In implementing a quality system, the first responsibility of management is to demonstrate its continual support. This support is demonstrated through management's leadership and participation, which is vital for a quality system to be effectively implemented and sustained. Organizations generally have standard ways to define authorities but may make modifications by delegation and role specification.

1) CFSAN's senior managers are committed to the development, implementation, maintenance, and improvement of a quality system that meets CFSAN customer needs, as well as regulatory and statutory requirements. They make their commitment evident by:
    a) Establishing and documenting the CFSAN quality system,
    b) Participating in QMS management reviews and follow-up actions, and
    c) Ensuring the availability of resources for conducting work and QMS processes including provision of a safe laboratory environment, appropriate scientific facilities and equipment, and an institutional system for the secure storage of scientific records.

2) CFSAN managers and directors demonstrate their commitment by:
    a) Establishing quality objectives that are derived from strategic priorities,
    b) Prioritizing, selecting, and approving written research plans that optimally utilize FDA resources to accomplish the mission of the Agency,
    c) Communicating the importance of customer satisfaction when fulfilling quality requirements,
    d) Participating in reviews of their unit's quality control activities and in follow-up actions, and
    e) Assuring communication, understanding, and implementation of the QS CFSAN-wide by providing appropriate training for staff, and monitoring compliance with this LQM.

Authority

To carry out strategic priorities and to meet established objectives, an organization's managers and staff need to know their responsibilities and authorities. An organization works more effectively when everyone knows who is responsible for what.

1) CFSAN uses several means to define and manage responsibility and authority:
    a) Organizational responsibilities of CFSAN components and the authorities to change responsibilities are defined within the FDA SMGs, Volume I, "Organizations and Functions."
    b) Chains of command, specific work process roles, and interrelationships are defined within readily accessible organizational charts and procedural documentation located on the CFSAN intranet.
    c) Authority and responsibility, but not accountability, may be delegated;

2) CFSAN managers direct and use the work and quality systems to accomplish organizational goals within the systems. According to their respective authorities, they may work on the systems by customizing procedures and instructions so that CFSAN maintains flexibility relevant to local circumstances.
   a) Managers are accountable within the chain of command for work accomplishments commensurate with their assigned authorities. Unit directors are accountable to customers and stakeholders for the quality of the work produced by their unit.
   b) Managers, including committee chairs, ensure that procedures are established and used to monitor adherence to work and quality system directives.
   c) Managers may delegate authority and responsibility, but retain accountability.
   d) A unit manager (director, deputy director, executive officer or equivalent) carries out duties for the unit. These duties may not be permanently delegated to staff or subordinate managers.

3) CFSAN supervisors ensure that planned work is accomplished and the quality system is adhered to — to ensure that staff perform their work generally within the established systems. They are accountable for ensuring that staff are knowledgeable of work and quality system procedures and tools. Supervisors are accountable for ensuring/performing many quality control functions.

Supporting information that will assist in fulfilling these requirements is:

- *CFSAN Organizational chart*

http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135673.htm

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Management Review

Senior management regularly reviews the quality system to ensure that it is working effectively, to take action for improvement, to increase efficiency, and to hold themselves and the organization accountable. Senior management conducts reviews of the quality system according to a planned schedule:

1) Reviews are more frequent for developing and immature systems
2) A minimum review frequency is once per year

Senior management reviews the quality system to ensure its continuing suitability, adequacy, and effectiveness.

1) Reviews include consideration of:
   a) The appropriateness of the quality policy and quality objectives,
   b) The suitability of policies and procedures for work and for the quality system,
   c) The results of audits and proficiency tests (when applicable),
   d) Customer feedback, including complaints,
   e) The analysis of process and product/service metrics (i.e., data selected to provide information needed about the quality of a process or product/service).
   f) The status of actions from previous management reviews, and
   g) Any changes in business practices or conditions that may affect the quality system, and the volumes or types of work.

2) The outcomes of such reviews may include:
   a) Improvements to the quality system and related quality processes,

b) Realignment of resources.

3) The results of management reviews are recorded and actions are tracked.

4) Management reviews and their outcomes are performed with, or communicated to, the QA Team.

Employee Responsibility

CFSAN employees shall operate according to the following:

1) Employees are accountable to their supervisors for the quality of their work and have a responsibility to initiate preventive action to minimize the occurrence of process failures or product nonconformities. Employees shall also identify and report quality problems so that corrective action can be initiated.
2) Staff members are encouraged to recommend process and product improvements.
3) Staff may be delegated quality-related duties such as QC responsibilities, peer assessment, records management, equipment maintenance, corrective actions, etc.
4) Staff selected for quality duties assist managers in establishing and maintaining the quality system either at a CFSAN-wide level or a unit level. Quality staff are accountable to their respective management representative.

3.0 NON-GLP LABORATORY STUDIES

(not intended to fall under the scope of 21 CFR Part 58)

3.1 Scope and Objectives

Scope
This section of the CFSAN Laboratory Quality Manual relates to laboratory studies conducted in and/or for CFSAN that are not intended to fall under the scope of 21 CFR 58 (Good Laboratory Practices for Nonclinical Laboratory Studies).

This section can be used in the development of a QS for basic and applied research; i.e., where the output is knowledge, information, data, or proof-of-concept. This QS covers biological, physical, chemical, and applied sciences, which use, for example, methods such as field investigation, laboratory experimentation, computer modeling, and theory formulation.

Objectives
Objectives of the Non-GLP Laboratory Studies section:
1. Provide information and policy related to studies conducted in and/or for CFSAN laboratories
2. Provide information related to Quality Systems and CFSAN Quality Assurance activities in relationship to non-GLP Studies

This section of the manual will serve as a guide to follow when performing non-GLP studies in CFSAN. It applies primarily to scientists and researchers and purposely uses scientific terminology in an attempt to translate the concepts of quality management into language that is more familiar to scientists.

This section provides guidance for the development and implementation of a QMS by scientists and supervisors in basic and applied research.

3.2 Roles and Responsibilities

This section presents information regarding the basic roles and responsibilities for CFSAN staff. The duties described below are not all-inclusive.

3.2.1 Office of Center Director

Establishes and manages a program to maintain quality and integrity for all Center laboratory studies and the processing of regulatory samples.

Responsibilities of the Office of the Center Director include:

1. Maintain a QA program to help ensure the quality and integrity of data produced by CFSAN.
2. Provide the resources and commitment to implement the LQM.
3. Develop overall CFSAN scientific policy and laboratory programs to support policy.
4. Review reports of CFSAN QA activities which include internal audit reports, corrective/preventive actions, management reviews, and continual improvement efforts.
5. Maintain overall responsibility to ensure that deviations and complaints are addressed.
6. Review and act on Institutional Animal Care and Use Committee (IACUC) recommendations.

3.2.1.1 Quality Assurance Team

The CFSAN Quality Assurance (QA) Team is responsible for managing the laboratory QA program. The QA Team assures management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the CFSAN LQM, best practices, and applicable requirements. QA personnel shall be entirely separate from and independent of the personnel engaged in the direction and conduct of laboratory studies and activities related to regulatory samples. These activities may vary among CFSAN facilities.

The QA Team shall perform the following:

1. Audit laboratories periodically and maintain written and properly signed records of each periodic inspection to ensure that quality standards are being met. The scope and frequency of these activities will be determined in consultation with senior management.
2. Periodically submit to management written status reports, noting any problems and the corrective actions taken.
3. Maintain and update the CFSAN Laboratory Quality Manual.
4. Maintain copies of all pertinent documentation and records.
5. Ensure that a CFSAN Automated Research Tracking System (CARTS) number has been assigned to each study upon approval (for projects with a duration of more than six months).
6. Audit laboratories in accordance with a predetermined schedule.

7. Generate QA status reports, which include internal audit reports, corrective/preventive actions, and continual improvement efforts.

Supporting information that will assist in fulfilling these requirements:

- *Draft Internal Audit Procedure*
- *Draft Management of External Inspections*
- *http://fdswa090.fda.gov:81/qa/sop.htm*

3.2.2 Principal Investigator (equivalent to Project Lead in CARTS)

For each laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the principal investigator (project lead). The principal investigator (project lead) has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation, and reporting of results. The principal investigator (project lead) shall be responsible for the following:

1. Developing the project/protocol and obtaining approval including using form 3244b *CFSAN Project Approval Record* or Form ASP01 Animal Study Protocol.
2. Ensuring that changes (amendments) to the project/protocol are documented.
3. Maintaining pertinent documentation regarding all project/protocol activities.
4. Communicating on a regular basis with contractors who provide project/protocol support.
5. Maintaining results of relevant analyses as part of the raw data for the project/protocol.
6. Documenting and addressing circumstances that may affect the quality and integrity of the laboratory study.
7. Preparing a final report (e.g., CARTS write-up, validated method, peer-reviewed publication, oral presentation, etc), in accordance with CFSAN policies.
8. Ensuring that raw data, documentation, protocols, specimens, and final reports (if necessary) are archived at the completion of a study.
9. Ensuring that the study is conducted in a safe manner and in accordance with the safety plan, safety procedures, and safety requirements.
10. Conducting the study in accordance with other relevant regulations, e.g. relating to the humane use of animals, radiation safety, controlled substance use, Human Subject treatment, chemical safety, etc.

3.2.3 Research Facility Management

For each laboratory study, research facility management shall:

1. Designate a principal investigator (project lead) before the study is initiated.
2. Replace the principal investigator (project lead) promptly if it becomes necessary to do so during the conduct of a study.
3. Ensure that projects/protocols are properly amended to reflect changes in responsible personnel.
4. Ensure that personnel clearly understand the functions they are to perform.

3.2.4 Veterinarian

The roles and responsibilities of CFSAN Veterinarians vary among CFSAN facilities. The following are basic duties of veterinarians (see IACUC and Animal Welfare Act for further guidance):
The veterinarian helps to ensure:

1. Adequate veterinary care is provided for animals used in research.
2. The health of laboratory animals used in studies and, therefore, the quality and integrity of research conducted by CFSAN.

Responsibilities are performed to a standard that complies with the regulations for proper animal care.

1. Serves as a clearing place for the ordering or all animals used in the research facility. Acclimates all animals obtained from approved outside vendors prior to use in laboratory studies.
2. Receives animals when delivered to a facility. Designates alternate to act when a Veterinarian is not available.
3. Documents the receipt, health status, housing, care, and feeding of research animals during the acclimation period.
4. Provides records of receipt, health certification, and release of animals to principal investigator at the end of the acclimation period.
5. Provides, upon request by the principal investigator (project lead), consultation and veterinary care to animals in the study, including oversight of surgical procedures and appropriate euthanasia procedures.
6. Establishes approved Standard Operating Procedures (SOPs) as necessary for receipt, housing, care, and feeding of animals while they are under control of the CFSAN Veterinarian. All SOPs developed for the care and use of laboratory animals must be provided with a protocol and be approved by IACUC during the protocol approval process.
7. Serves as a member of the CFSAN Institutional Animal Care and Use Committee (IACUC).
8. Provides training for animal care to all CFSAN employees and contractors in MOD 1.

Supporting information that will assist in fulfilling these requirements is:

- *Office of Laboratory Animal Welfare (OLAW) guidance http://grants.nih.gov/grants/olaw/olaw.htm*
- *Animal Welfare Act (AWA) www.nal.usda.gov/awic/legislat/usdaleg1.htm*
- The *Guide for the Care and Use of Laboratory Animals* guidance *www.aaalac.org/*

3.2.5 FDA Facilities Operations and Engineering Management

The Office of Real Property Services enhances the quality and integrity of laboratory work conducted at CFSAN by carrying out the responsibilities listed below. These activities may vary among CFSAN facilities.

1. Serves as project oversight on all contracts whose obligations are to provide all aspects of building maintenance for systems and equipment relating to laboratory operations. This includes, but is not limited to, room and fume hood airflow, cold box and structural maintenance (walls, ceilings, floors), water, gas, and electrical services.
2. Provides guidance for the maintenance of all CFSAN-installed equipment. This includes offering technical assistance, making recommendations, and preparing requisitions necessary to contract for the required services.
3. Provides assistance and recommendations on space utilization and assists in relocations.
4. Provides a mechanism for the control of vermin.

3.2.6 Warehouse/Storeroom Services Contractors

The Warehouse/Storeroom Services Contractor enhances the quality and integrity of the laboratory work conducted at CFSAN by carrying out the responsibilities listed below. These activities may vary among CFSAN facilities.

1. Receives and distributes laboratory and other supplies ordered for use.
2. Operates and maintains the FDA Scientific Supply Store.
3. Arranges for the shipment of appropriately packaged items, with the possible exceptions of radioactive materials and select agents and toxins, to their destination via GSA contract-approved transportation company or courier service.
4. Delivers gas cylinders and picks up empty gas cylinders upon request of laboratory personnel.
5. Provides for pick up, processing, and transportation of medical waste to a centralized location for disposal.
6. Receives and stores equipment and supplies for use in the limited access areas at designated facilities.

3.2.7 Institutional Animal Care and Use Committee

The Institutional Animal Care and Use Committee (IACUC) enhances the quality and integrity of the laboratory work conducted at CFSAN by carrying out the responsibilities listed below to ensure that animals utilized in CFSAN research are humanely treated with minimization of pain and discomfort (see Animal Welfare Act for further guidance). In addition, as agreed to by AAALAC, the Dauphin Island and Moffett Facilities are inspected once a year when animals are on study.

1. Reviews CFSAN's animal research program at least once every 6 months using the *Guide for the Care and Use of Laboratory Animals* as a basis and submits reports of the status for the Institutional Official.
2. Inspects all animal facilities including animal study areas at least once every 6 months using the *Guide for the Care and Use of Laboratory Animals* as a guide and submits reports of the status to the Institutional Official.

3. Prepares reports of IACUC evaluations and submits the reports to the Institutional Official.
4. Reviews and investigates concerns involving the care and use of animals at CFSAN's research facilities resulting from public complaints or from reports of noncompliance received from facility personnel.
5. Makes recommendations to the Institutional Official regarding any aspect of CFSAN's animal program, animal facilities or personnel training.
6. Reviews and approves proposed activities related to the care and use of animals included in the protocol, protocol amendments, and standard operating procedures.
7. Suspends any activity involving animals when necessary if approved procedures are not followed.
8. Approves changes in study personnel involved in animal studies.

Supporting information that will assist in fulfilling these requirements is:

- *CFSAN Building and Laboratory Services*
  http://inside.fda.gov:9003/CFSAN/OfficeofManagementSystems/ucm010818.html
- *Office of Laboratory Animal Welfare (OLAW) guidance*
  http://grants.nih.gov/grants/olaw/olaw.htm
- *Animal Welfare Act (AWA) www.nal.usda.gov/awic/legislat/usdaleg1.htm*
- The *Guide for the Care and Use of Laboratory Animals* guidance
  www.aaalac.org/

3.2.8 Animal Husbandry Contractor

The Animal Husbandry Contractor enhances the quality and integrity of animal studies conducted at CFSAN by carrying out the responsibilities listed below. These activities may vary among CFSAN facilities.

1. Provides all personnel to perform animal husbandry services.
2. Provides technical support to the Veterinarian in acclimation services and procedures.
3. Performs daily observations to assess condition of animals housed in the environmentally controlled Animal Facility that uses supply/return corridor system.
4. Monitors and records the environmental conditions (temperature, humidity, and directional air flow) of all active animal rooms and support areas.
5. Sanitizes and prepares the receiving dock to receive animal shipments into the facility and verifies accompanying documents.
6. Provides sufficient personnel to ensure that fresh feed and water are available to laboratory animals.
7. Operates tunnel and rack washers to provide clean cages, water bottles, litter pans, etc., in support of animal studies.
8. Provides support for technical procedures upon request of the principal investigator (project lead).

9. Decontaminates, sanitizes, and maintains all animal rooms and environmentally controlled facilities that use supply/return corridor system passageways in a manner that ensures a proper environment for conducting animal studies.
10. Develops and maintains SOPs outlining the duties for areas covered by the Animal Husbandry Services Contract.
11. Participates in pre-study meetings that require interaction with other contract and government study personnel.

3.2.9 Glassware Contractor

The glassware contractor enhances the quality and integrity of the laboratory work conducted at CFSAN by carrying out the responsibilities listed below. These activities may vary among CFSAN facilities.

1. Maintains a central facility for the cleaning and storage of laboratory glassware.
2. Provides a mechanism for the ordering of specialized or new standard laboratory glassware.
3. Provides delivery of clean glassware and the pickup of dirty glassware.
4. Provides the storage, handling and distribution of sterile laboratory glassware.

3.2.10 Media Services Contractors

The media services contractors enhance the quality and integrity of the laboratory work conducted at CFSAN by carrying out the responsibilities listed below. These activities may vary among CFSAN facilities.

1. Prepares and distributes sterile culture media.
2. Prepares and distributes selected buffers and saline solutions.

3.2.11 Safety Office

The Safety Office ensures that all laboratory work conducted at CFSAN is performed in compliance with all applicable occupational safety and health and environmental management regulations, standards and CFSAN policies.

Supporting information that will assist in fulfilling these requirements is**:**

- *http://inside.fda.gov:9003/CFSAN/OfficeofManagementSystems/ucm040820.html*
- *Draft Materials Management SMG*

3.3 Personnel Development

This section provides direction to effectively manage human resources. Refer to pertinent sections of the SMG 2020, Section 2, Resource Management.

Personnel, including laboratory personnel need to be qualified for the duties they perform. The involvement and support of personnel will result in improving both organizational and quality system effectiveness and efficiency.

Management shall:

1. Develop and/or use detailed position descriptions that include responsibilities and authorities and discuss with personnel so that an employee's level of empowerment is understood.
2. Provide training on:

   a. FDA, organization, and unit orientation, including
      - mission and goals,
      - ethics and conflict of interest, and
      - information disclosure;

   b. Policies, processes, procedures, and written instructions related to
      - work activities,
      - the product/service, and
      - the quality system.

   c. Key strategies and methods that support the desired work culture (team building, communication, change, behavior).

      - Ensure that skills gained from training are incorporated into day-to-day performance. This may require:
        - additional certification, or
        - specific authorizations to perform work activities.
      - Maintain training, certification, and/or authorization records.
      - Encourage communication by acting upon suggestions and developing empowered cross-cutting communities to share and improve common practices.

3.4 Project Planning, Protocols, and Procedures

3.4.1 Project Planning

All research projects with a duration of greater than six months, that involve CFSAN personnel are to be posted in the CFSAN Automated Research Tracking System (CARTS) via the CFSAN Intranet. CARTS provides a mechanism for approval of projects by CFSAN management, as well as the sharing of information and tracking of progress on research and activities being conducted in CFSAN.

Procedures for planning and conducting research projects should include:

- Review of the relevant literature
- Determination of overall objectives
- Development of the experimental approach

- Determination of resource needs, including equipment, supplies, personnel, and budget
- Approval by management for conducting work with adequate and available resources
- Preliminary experimentation to develop protocols (if necessary)
- Determination of critical control points (areas) to monitor and ensure quality
- Documentation of raw data in an official laboratory notebook or similar record
- Determination of project milestones with timeline for completion
- Development of safety procedures and plans, including waste disposal, if applicable

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Supporting information that will assist in fulfilling these requirements is:

- *CSFAN QA SOPs*
  http://fdswa090.fda.gov:81/qa/sop.htm
- *Management and Use of CFSAN Official Laboratory Notebooks-SMG*
  http://fdswa090.fda.gov:81/qa/labnotebook.pdf
- *Initiation and Submission of CFSAN Project Approval Form 3244b*
  http://fdswa090.fda.gov:81/qa/sop_3244b_project_approval.pdf
  http://fdswa090.fda.gov:81/qa/FDA_3244b.pdf

Laboratory research projects are to be posted in CARTS according to the currently accepted procedures; periodic progress reports should be prepared as requested by management.

Principal investigator(s) (CARTS project lead(s)) shall prepare appropriate documents for studies (e.g. CARTS, FDA form 3244b, ASP01) according to CFSAN policy. In contrast to protocols for animal studies and in vitro GLP studies, many protocols developed in non-GLP studies are documented in "Official" laboratory notebooks. Such protocols ensure that a study can be repeated or reconstructed, if necessary.

- Protocols for studies involving the use of animals shall be reviewed by the Institutional Animal Care and Use Committee (IACUC) to ensure that animals utilized in CFSAN research are humanely treated, with minimization of pain and discomfort.
- All protocols using select agents and toxins will be reviewed by the site-specific Responsible Official or Alternate Responsible Official.
- All protocols using radioisotopes will be reviewed by the Radiation Safety/Protection Officer.

Protocols are to be retained with the study records. It is the responsibility of the project lead to maintain a record of an approved project/protocol. Modifications to approved protocols involving the use of animals must be made promptly by the principal investigator (project lead) using the CFSAN - *Protocol Amendment form* (FDA 3244a). Protocol Amendments must be submitted to the appropriate authorities in a timely manner. Additionally, amendments to a protocol that involve changes or addition to animal procedures must be approved by IACUC prior to being submitted to the QA Team. Significant changes to the protocol that deviate from the approved safety plan, procedure or protocol or otherwise increase the nature of the hazard must be approved in advance by the Safety Office and Responsible Official/Alternate Responsible Official (if applicable).

All changes in, or revisions of, an approved project/protocol shall be made promptly by the principal investigator (project lead), and dated; for animal studies, such changes must be signed and dated by the IACUC Chairperson and maintained with the protocol.

CFSAN Form Guidance

	GLP	Non-GLP
Studies involving animals	Form ASP01 and CARTS	Form ASP01 and CARTS
Studies not involving animals	FDA Form 3244b and CARTS	FDA Form 3244b and CARTS

Supporting information *that will assist in fulfilling these requirements is:*

- *42 CFR part 73 (HHS-CDC)**,** Possession, Use, and Transfer of Select Agents and Toxins.*
- *7 CFR part 331 (USDA), Agricultural Bioterrorism Protection Act.*
- *9 CFR part 121 (USDA), Possession, Use and Transfer of Biological Agents and Toxins.*
- *MOD-1 Select Agent Registration.*
- *FDA Form 3244b, CFSAN Project Approval Form*

http://fdswa090.fda.gov:81/qa/FDA_3244b.pdf

- *SOP 3244b, Initiation and Submission of CFSAN Project Approval Form 3244b.*

http://fdswa090.fda.gov:81/qa/sop_3244b_project_approval.pdf

- *Form ASP01, Animal Study Protocol*
- *FDA Records Control Schedule*

http://inside.fda.gov:9003/it/RecordsManagement/RetentionInstructions/ucm023400.html

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3.4.2 Standard Operating Procedures (SOPs)

Standard operating procedures describe the way specific operations and methods are to be performed. These may include sampling operations, sample preparation, calibrations, measurement procedures, and any operation that is done on a repetitive basis. Peer-review of all methodology is a minimum requirement to ensure understandability and to enhance continuity of a measurement process, as well as to receive the benefit of technical feedback.

Laboratories shall have SOPs for routine operations/testing. SOPs shall be written and approved by authorized individuals. SOPs may consist of peer reviewed scientific methods, and manufacturers or contractors SOPs. Such SOPs help ensure the quality and integrity of the data generated. A historical file of SOPs and all revisions shall be maintained.

SOPs shall be:

- readily available to study personnel,
- prepared by authorized personnel (e.g., Veterinarian, animal housing unit, etc..),
- developed for routine or repetitive laboratory tasks, as necessary,

- maintained, filed, and distributed in a manner in which all necessary personnel have access.

Supporting information that will assist in fulfilling these requirements is:

- *Division Laboratory Quality Control Plans*

3.5 Facilities

3.5.1 General
Each research facility shall be of suitable size and construction to facilitate the proper conduct of laboratory studies. It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.

3.5.2 Animal Care Facilities
Guidelines of the Institutional Animal Care and Use Committee (IACUC) are to be followed, when studies involve animals, to ensure that the study is conducted in compliance with animal care and animal facilities guidelines.

3.5.3 Animal Supply Facilities
There shall be storage areas, as needed, for feed, bedding, supplies, and equipment. Storage areas for feed and bedding shall be separated from areas housing the test systems and shall be protected against infestation or contamination. Perishable supplies shall be preserved using appropriate means. Facility Operations and Engineering Management provides assistance and recommendations on space utilization, provides assistance with relocations, and maintains air quality and air flow, temperature, and humidity for the testing facility.

3.5.4 Laboratory operation areas
Separate laboratory space shall be provided, as needed, for the performance of routine and specialized procedures required by laboratory studies.

3.5.5 Archiving specimens and data
Space shall be provided for archives, limited to access by authorized personnel only, for the storage and retrieval of raw data and specimens from completed studies, as necessary. (Interpretation of what constitutes “raw data” for non-GLP studies is less rigorous than the definition found in 21 CFR part 58.)

3.5.6 Laboratory Housekeeping
CFSAN laboratories shall be maintained in a clean and orderly fashion to help ensure the quality and integrity of the data generated. Specific procedures necessary to maintain laboratory areas shall be developed, as necessary.

Responsibilities are presented below:

Laboratory personnel

Laboratory personnel shall be held accountable for maintaining a neat, clean, and uncluttered work area. This shall include taking steps to ensure that benches, cabinets, ceilings, walls, and floors are kept clean and free of clutter and that any unused or nonfunctional equipment is promptly and properly stored and/or permanently removed.

Laboratory supervisors

Supervisors shall ensure that personnel properly maintain neat and clean working areas. This shall include taking steps to ensure that benches, cabinets, ceilings, walls, and floors are kept clean and free of clutter and that any unused or nonfunctional equipment is promptly and properly stored and/or permanently removed. Supervisors are responsible for ensuring that any deficiencies are corrected.

Principal investigators

Principal investigators (project leads) in conjunction with line management shall ensure that all units involved in laboratory studies have proper housekeeping procedures to help ensure the quality and integrity of study data. The principal investigator(s) (project lead(s)) will discuss any deficiencies with unit management.

3.6 Materials

3.6.1 Reagents and Solutions

The responsibility of managing reagents and solutions is that of the scientists and their immediate supervisors. Reagents, solutions, chemicals, and media shall be treated as follows:

1. All reagents and solutions in the laboratory areas should be managed appropriately and labeled to indicate identity, titer or concentration, storage requirements, and expiration date.

2. Deteriorated or outdated reagents and solutions should not be used and shall be properly disposed of in accordance with standard operating procedures while observing all safety precautions.

3. Purchased chemicals, solutions, media, and reagents should be received and tracked according to the Materials Management SOP.

4. Solutions and other reagents prepared in the laboratory shall also be labeled to indicate date of preparation and the preparer's initials. Other information that may be pertinent should also be indicated on the label.

5. Reagents and solutions that contain hazardous components and require special protective measures while handling and storing (e.g., need for protective equipment, use in a hood, peroxide-forming compounds that pose acute safety hazards, etc) shall have an appropriate warning sticker affixed to each container.

Supporting information that will assist in fulfilling these requirements is:

- *Draft Materials Management Procedure*

- *Division Laboratory Quality Control Plan*

3.7 Equipment

CFSAN shall maintain equipment inventories, as well as controls for equipment used for testing or measuring. CFSAN research units shall ensure that appropriate validation, calibration, maintenance, and monitoring of equipment conform to appropriate scientific standards or applicable regulatory requirements and laws.

The principal investigator (project lead) is responsible for the following:

a. Removal of equipment from service when not functioning appropriately or when calibration or maintenance has not been performed (i.e., placement of a sign on equipment indicating that it is out of service).
b. Contacting appropriate group for assessment and/or repair when equipment is not functioning appropriately.
c. Developing and maintaining schedule and records for the maintenance and calibration of equipment.
d. Performing tasks to monitor equipment validation, calibrations, and maintenance.
e. Maintaining control of equipment user manuals.
f. Reviewing data and records related to equipment.

Additional information regarding equipment design, maintenance, and calibration may be found in the Equipment Management SOP.

Supporting information that will assist in fulfilling these requirements is:

- *Draft Equipment Management Procedure*
- *Division Laboratory Quality Control Plan*

3.8 Training, Education, and Experience

Employee training is an integral part of the process necessary for best laboratory practices. Training should be conducted in a consistent manner. New employees must have adequate training with respect to the general policies and processes of quality assurance, as well as be trained, as necessary, for their specific position duties and responsibilities.

Management (immediate supervisor and/or Office Director) shall ensure that each individual engaged in the conduct of, or responsible for, the supervision of a laboratory study shall have education, training, and experience, or a combination thereof, to enable the individual to properly perform the assigned duties. Training and education includes, but is not limited to the following:

- Quality assurance training consistent with duties and responsibilities
- Policies contained in this Manual
- Training in best laboratory practices and procedures needed to do relevant laboratory work

- Safety training consistent with duties and responsibilities

Methods of demonstrating competency include:
- Discussions/reviews with employee
- Performance/direct observations
- Written and/or oral examination

Management (immediate supervisor and/or Office Director) shall ensure that a current summary of training and experience for each individual engaged in or supervising the conduct of a laboratory study is maintained. Training and experience can be documented by curriculum vitae, resumes, training certificates, etc.

Staff College shall be responsible for maintaining records of training activities it has provided (DHHS sponsored courses are captured in the Learning Management System) and names of those who attended those courses. For non-DHHS courses, individual employees and /or supervisor shall be responsible for retaining documentation of training (e.g., training certificates, attendance rosters) and providing this information to designated individual(s), usually the immediate supervisor. The immediate supervisor will maintain and ensure that these records are kept in an organized manner and are readily available upon request.

Supporting information that will assist in fulfilling these requirements is:
- *CFSAN Staff College*
  http://inside.fda.gov:9003/EmployeeResources/Training/StaffCollegeCFSAN/default.htm

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3.9 Documents and Records

Laboratory research data are the essential components of scientific progress, and scientific integrity requires meticulous attention to their acquisition and maintenance. Primary data include data in notebooks, printouts, computer-based storage devices, photographs, slides, negatives, films, scans, images, auto-radiograms, electrophysiological recordings, gels, blots, printed records, observations and notes, electronic data, video and audio records, spectra, samples, specimens, and other materials that contain raw unprocessed information collected during the research process. Secondary data include various representations and summaries of the primary data such as statistical analyses, graphic charts, data tables, and conclusions.

a. All laboratory research should be carefully documented in a form that will allow access for analysis and review by collaborators and supervisors at any time. Investigators should be aware that research data are legal documents for: establishing research priority and patent rights; allowing independent re-analysis of the data; supporting the veracity of published results against challenges; supporting regulatory decision-making; and satisfying data requests of congressional committees and courts of law.

3.9.1 Creation of Data and Records

Research data generated in or for CFSAN are the property of the FDA.

All primary data and observations should be stored permanently; the format used will depend on the type of data.

"Official" Laboratory Notebooks

Official laboratory notebooks are the preferred medium for recording laboratory data. However, other forms of documentation such as forms, diagrams, and electronic media, may replace or be used in conjunction with laboratory notebooks with appropriate cross-referencing. All electronic data outputs should have a system for documentation, cross-referencing, backup, and storage of the work (i.e., copying files to a shared drive, a second hard drive, or other optical or magnetic media).

The management of "official" laboratory notebooks is the responsibility of the Office Director or their designee. Each office will be responsible for procuring, distributing and tracking the notebooks as described in the CFSAN staff manual guide titled "Use and Management of CFSAN Official Laboratory Notebooks."

A laboratory notebook assigned to an employee who is separating from the laboratory and/or the FDA must be turned in to the first line supervisor, who will be responsible for maintaining the notebook and other research information. Also the Agency guidance titled, FDA Record Control Schedule.

Standard laboratory practices, described below, regarding recording of data shall be followed:

- Data generated, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in indelible ink in the provided laboratory notebook.
- Any change in entries shall be made so as not to obscure the original entry and shall be dated and initialed.
- In automated data collection systems, the individual responsible for direct data input/collection shall be identified at the time of data input/collection.
- Data collected as output from an instrument (i.e., images, instrument printouts, etc.) should be either saved permanently as a hardcopy fastened with a permanent attachment to a consecutive page in the laboratory notebook, or recorded in an approved non-modifiable electronic file (such as a read-only CD or a signed and certified pdf files) whose location and identification is documented in the laboratory notebook.
- Any change in automated data entries shall be made so as not to obscure the original entry and shall be dated, and the responsible individual shall be identified.
- Specimens, cells or samples collected should be individually identified; an entry in the permanent record (e.g., laboratory notebook) should describe the relevant sample information, storage conditions and location of the samples.
- Data received from collaborators or other sources outside an investigator's

laboratory should be labeled with the date of receipt and catalogued in a laboratory notebook entry which identifies where the data are stored.

3.9.2 Archiving of Data

Archived laboratory records (e.g. CARTS, official notebooks, official samples) will be managed according to the type of record. These archives shall:

1. Provide for orderly storage and expedient retrieval of archived raw data, documentation, protocols, specimens, and interim and final reports. (Interpretation of what constitutes "raw data" for non-GLP studies is less rigorous than the definition found in 21 CFR part 58.)

2. Provide conditions of storage which minimize deterioration of the documents or specimens

3.9.3 Retention of Records

Relevant raw data, documentation, projects/protocols, final reports, and specimens generated in the conduct of a "significant" research project shall be retained permanently, according to the FDA Records Retention Schedule.
http://inside.fda.gov:9003/it/RecordsManagement/RetentionInstructions/ucm168510.htm

Relevant raw data, documentation, projects/protocols, final reports, and specimens generated in the conduct of a "non-significant" research project shall be retained for a period of 30 years, according to the FDA Records Retention Schedule.
http://inside.fda.gov:9003/it/RecordsManagement/RetentionInstructions/ucm168512.htm

The following documents (originals or true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records) shall also be retained for a period of not less than six years from the date of approval of the final report:

1. Copies of protocols and records of quality assurance inspections shall be maintained by the QA Team as a readily accessible system of records.
2. Documentation of training and experience and position descriptions as described in this Manual (i.e., training, education, and experience).
3. Records and reports of the maintenance and calibration and inspection of equipment as described in this manual (i.e., equipment).

3.10 Reporting Research

CFSAN scientists are encouraged to submit their findings for publication in scientific journals so that the products of CFSAN research are accessible to the FDA and the public.

External publication

a. Manuscripts intended for publication outside of the FDA and Final Reports for internal archiving must be cleared before they are submitted. The manuscript/report, along with the Request for Clearance form (attached as Appendix I), must be presented to supervisors for review and approval, consistent with the Agency's manuscript clearance procedures.
b. The author must follow a Center-approved procedure for linking the published findings to original data collected in the FDA lab.

Internal Reporting

a. FDA research that is completed but not published in a scientific journal should be documented in a Final Report (hardcopy or electronic) to assure that the results of FDA-funded research are recorded in a standard manner and accessible within the Agency. Final Reports should be written when a research goal is completed and resources are redirected to other work. Final Reports do not need to be written to describe experiments that were technically defective, or exploratory research that did not achieve meaningful results. Support experiments that were performed during the course of a published research project but were not described in any publication need not be described in a Final Report unless the investigator believes that the results could be of future use to the FDA.

b. Final Reports should be approved using the Request for Clearance of Manuscript or Final Report Describing Laboratory Research Conducted at FDA form (or similar), and should include an appended Original Data Index or the signature of a Division Director (or designee) verifying that the findings described in the Final Report are supported by the original data.

Supporting information that will assist in fulfilling these requirements is:

- *Use and Management of "Official" Laboratory Notebooks SMG http://fdswa090.fda.gov:81/qa/labnotebook.pdf*
- *FDA Records Control Schedule http://inside.fda.gov:9003/it/RecordsManagement/RetentionInstructions/default.htm*
- *Draft SMG title, "Minimum Standards for the Conduct of Laboratory Research at the FDA"*

3.11 Conduct of Studies, Ethics, and Confidentiality

3.11.1 Conduct of Studies

Studies conducted, in whole or in part at or for CFSAN, shall be conducted according to current CFSAN laboratory guidelines and in concurrence with quality standards presented in this manual.

It is the responsibility of all individuals involved in the conduct of a study to ensure that all data are recorded appropriately and that corrections to recorded data are made appropriately. Additional responsibilities related to the conduct and documentation of studies are presented below.

The principal investigator (project lead) shall:

- Ensure that procedures indicated in an approved protocol are followed by study personnel.
- Ensure that appropriate documentation is maintained to support the results of the research conducted.

Managers shall:

- Review the progress of research conducted in their area on a periodic basis.

Laboratory personnel shall:

- Take necessary personal sanitation and health precautions designed to avoid compromising the research environment.
- Wear clothing and other personal protective equipment appropriate for the duties they perform. Such clothing and equipment shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination.
- Report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on the study.

Ethics

To best serve customers, stakeholders, and employees, an organization's managers and staff need to be free of undue internal and external pressures that may adversely affect the quality of their work. Ethics standards promote and strengthen confidence in the integrity of the organization. CFSAN managers and supervisors shall strive to ensure that federal, departmental, and FDA ethical standards are understood and followed by employees.

Supporting information that will assist in fulfilling these requirements is:

- *"FDA Ethics Program"*
  http://inside.fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/default.htm

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Confidentiality

To serve its customers, an organization protects information from inappropriate release or misuse while maintaining appropriate transparency in their operations. CFSAN managers and supervisors shall strive to ensure that information disclosure, liabilities, responsibilities, and procedures are understood and followed by employees.

Supporting information that will assist in fulfilling these requirements is:

- *FDA SMG 2280.10, Protection of Non-Public Information*
- *FDA/CFSAN Freedom of Information - http://www.fda.gov/foi/*

3.12 Audits

Information regarding monitoring processes, conducting and/or participating in audits and inspections, as well as verifying data generated during the conduct of laboratory activity and handling of regulatory samples, are critical elements of a quality system.

An organization undergoes audits and/or assessments to determine whether its quality system conforms to applicable requirements and is effectively implemented and maintained: audits evaluate the quality system. Actions taken based on audit results can enhance strengths and reduce weaknesses in an organization.

CFSAN participates in internal audits and external inspections on a periodic basis. Internal audits are performed to measure strengths and weaknesses in actual performance against CFSAN procedures, methods, or applicable standards, including safety standards. External inspections are performed to demonstrate to the inspection organization that CFSAN is in compliance with applicable rules, regulations, and guidelines.

The QA Team will be responsible for the following auditing activities (internal and external):

- Developing and documenting internal audit procedures
- Developing and documenting external inspection procedures
- Ensuring that managers responsible for the areas audited take timely action on resolving audit findings
- Ensuring that follow-up activities are completed, verified, and recorded
- Ensuring that the audit reports are forwarded to senior management in a timely manner

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Supporting information that will assist in fulfilling these requirements is:

- *Draft Internal Audit Procedure*
- *Management of External Inspections*
- *Draft Corrective/Preventive Action Procedure*

3.13 Corrective/Preventive Actions

Corrective Actions

When quality-related problems and issues are identified, the organization resolves them and prevents them from recurring. Problems may be identified through data analysis, audit and proficiency reports, management review meetings, complaints, customer satisfaction queries, or internal feedback.

Corrective action includes evaluation of the significance of the problem and the impact on operating costs, error costs, product fitness, and customer satisfaction.

- CFSAN managers shall ensure that documented procedures are maintained to investigate root causes of nonconformities and complaints, to implement effective corrective action to prevent recurrence, and to prepare summaries for management review.
- CFSAN managers shall ensure that corrective action is taken in reaction to a significant risk to quality or a departure from an established procedure.

Preventive Actions
Quality is most efficiently achieved by preventing problems from occurring rather than detecting problems afterwards. Prevention is based on quality and process planning, process control, training, and other aspects of the quality system. Results of data analysis, changes in organization, or changes in the operating environment may suggest potential problems. The need for preventive actions is based upon the significance and impact of the potential problem.

- CFSAN managers shall ensure that CFSAN establishes and maintains documented procedures to identify the root causes of potential quality problems, to select the necessary deterrents so that the problem does not occur, and to prepare summaries for management review.
- The CFSAN managers shall ensure that preventive action procedures are used proactively when significant risks of possible problems are identified.

Supporting information that will assist in fulfilling these requirements is:

- *Draft Corrective/Preventive Action Procedure*

3.14 Continual Improvement

A quality system is an integral part of a dynamic, growing organization. CFSAN managers shall continually improve the quality system. Improvements may be reactive (corrective) or proactive (preventive).

- The CFSAN QMS uses tools outlined in this Quality Manual — the quality policy and objectives, process measurements, data analysis, feedback, audit results, corrective and preventive actions, and management reviews — to facilitate continual improvement. Continual improvement encompasses both incremental improvements within the existing processes and major changes in process redesign.
- CFSAN managers shall ensure that preventive action procedures are used proactively when significant risks of possible problems are identified.

Documenting Complaints

CFSAN shall maintain a process for documenting complaints related to issues that may impact the quality system, as well as complaints initiated from the research staff regarding quality issues.

Supporting information that will assist in fulfilling these requirements is:

- *Anonymous CFSAN Employee Suggestions (ACES) http://intranet.cfsan.fda.gov/aces/*

Quality Monitoring

Quality monitors are specific performance measurements or indicators designed to monitor one or more processes during a defined time and are useful for evaluating progress.

- In accordance with the scope and objectives set by responsible officials, the QA Team identifies quality indicators (as exemplified by elements in QA Internal Auditing Checklist) to monitor the performance of selected processes and maintains processes and schedules for collection and evaluation of quality indicator data.
- Quality monitors are defined for short-term and long-term audits of processes.
- Quality monitors are adopted as needed based on the current events of CFSAN to monitor deviations and nonconformances.
- Quality monitors can be defined by various management groups to evaluate the effectiveness of CFSAN's policies, processes, and procedures.

3.15 Studies Performed Under Grants and Contracts

Laboratory work conducted under a grant or contract for CFSAN must conform to Agency requirements outlined in the Staff Manual Guides listed below.

Supporting information that will assist in fulfilling these requirements is:

- *SMG 2610.1- Acquisition of Supplies and Services Under Contracts* (http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm162041.htm)
- *SMG 2150.2 – Grants Management – Grants and Cooperative Agreement* (http://inside.fda.gov:9003/PolicyProcedures/StaffManualGuide/VolumeIIIGeneralAdministration/ucm007150.html)

4.0 GLP (mainly 21 CFR Part 58)

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4.11 Project Reporting

4.12 Audits

4.1 Scope and Objectives

Scope
This section of the CFSAN Laboratory Quality Manual relates to nonclinical laboratory studies conducted in CFSAN that are intended to fall, in part, under the scope of 21 CFR 58 (Good Laboratory Practices for Nonclinical Laboratory Studies).

Objectives of GLP Nonclinical Laboratory Studies section:
1. Provide information and policy related to 21 CFR 58 among other guidance documents.
2. Provide information and policy related to nonclinical laboratory studies conducted in CFSAN laboratories.
3. Provide information related to Quality Systems and the CFSAN Quality Assurance Unit.

4.2 Roles and Responsibilities

4.2.1 Office of Center Director

Establishes and manages a program to maintain quality and integrity for all Center laboratory studies and the processing of regulatory samples, and ensures that all Center laboratory studies subject to FDA's Good Laboratory Practice regulations are conducted in compliance with them.

Responsibilities of the Office of the Center Director include:
1. Maintain a QA program to help ensure the quality and integrity of data produced by CFSAN.
2. Provide the resources and commitment to implement the LQM.
3. Developing overall CFSAN scientific policy and laboratory programs to support policy.
4. Review reports of CFSAN QA activities which include internal audit reports, corrective/preventive actions, management reviews, and assessing continual improvement efforts.
5. Maintain overall responsibility to ensure that all GLP deviations and complaints are addressed.
6. Serve as the final decision point for determining which studies are subject to GLP regulations.
7. Reviews and acts on IACUC recommendations.

4.2.1.1 Quality Assurance Unit

A testing facility shall have a QA Unit which shall be responsible for monitoring each study to assure management that the facilities, equipment, personnel, methods, practices, records, and controls are in conformance with the regulations. For any given study, the quality assurance unit shall be entirely separate from and independent of the personnel engaged in the direction and conduct of that study. The QA Unit shall submit periodic reports to the Office of the Center Director on status of GLP studies and maintain the CFSAN Laboratory QA Manual.

The QA Unit shall perform the following:

1. Maintain a copy of a master schedule sheet of all nonclinical laboratory studies conducted at the testing facility, indexed by test article and containing the test system, nature of study, date study was initiated, current status of each study, identity of the sponsor, and the name of the study director.
2. Maintain copies of all protocols pertaining to all nonclinical laboratory studies for which the Unit is responsible.
3. Ensure that a CFSAN CARTS number has been assigned to each study, upon approval.
4. Inspect each nonclinical laboratory study at intervals adequate to ensure the integrity of the study and maintain written and properly signed records of each periodic inspection showing the date(s) of the inspection, the study inspected, the phase or segment of the study inspected, the person performing the inspection, findings and problems, action recommended and taken to resolve existing problems, and any scheduled date for reinspection. Any problems found during the course of an inspection that are likely to affect study integrity shall be brought to the attention of the study director and management promptly.
5. Periodically submit to management and the study director written status reports on each study, noting any problems and the corrective actions taken.
6. Determine that no deviations from approved protocols or standard operating procedures were made without proper authorization and documentation.
7. Review the final study report to ensure that the report accurately describes the methods and standard operating procedures, and that the reported results accurately reflect the raw data of the nonclinical laboratory study.
8. Prepare and sign a statement to be included with the final study report that shall specify the dates inspections were made and findings reported to management and to the study director.
9. Monitor all GLP studies for, but not limited to, the following:
   a. Characterization of test and control articles and records maintained.
   b. Correction of deviations.
   c. Labeling of reagents.
   d. Identification of animals.
   e. Labeling of storage containers for test and control articles.
   f. Storage of reserve samples of test and control articles and records maintained.
   g. Records for identification, receipt, and distribution of study samples and test and control articles.
   h. Testing performed for homogeneity, stability, and concentration of test article/carrier mix and testing records maintained.
   i. Adherence to protocol(s) and standard operating procedures.
   j. Labeling of specimens.
   k. Recording of data.
   l. Retention of raw data.
10. Document compliance/noncompliance of study director in performing all required functions.
11. Accompany external investigators during inspections and audits of CFSAN nonclinical laboratory (GLP) studies.

4.2.2 Testing Facility Management

For each GLP laboratory study, testing facility management shall:

1. Designate a study director as described in 21 CFR 58.33 before the study is initiated (§ 58.33 is presented later in this document).
2. Replace the study director promptly if it becomes necessary to do so during the conduct of a study.
3. Ensure that study protocols are properly amended to reflect changes in responsible personnel, e.g., study director and principal investigator(s) (project lead(s)).
4. Ensure that there is a Quality Assurance Unit as described in 21 CFR 58.35.
5. Ensure that test and control articles or mixtures have been appropriately tested for identity, strength, purity, stability, and uniformity, as applicable.
6. Ensure that personnel, resources, facilities, equipment, materials, and methodologies are available as scheduled.
7. Ensure that personnel clearly understand the functions that they are to perform.
8. Ensure that any deviations from these regulations reported by the Quality Assurance Unit are communicated to the study director and that corrective actions are taken and documented.

4.2.3 Study Director

For each nonclinical laboratory study, a scientist or other professional of appropriate education, training, and experience, or combination thereof, shall be identified as the study director. The study director has overall responsibility for the technical conduct of the study, as well as for the interpretation, analysis, documentation, and reporting of results, and represents the single point of study control. The study director shall be responsible for the following:

1. Written commitments from support units, including contract support, in planning studies prior to protocol approval.
2. Development of the study protocol and obtaining approval using FDA Form 3244b or Form ASP01.
3. Changes to the protocol are processed according to 21 CFR 58.120 as well as CFSAN policies, and submitted to the QA Unit (See Form 3244a).
4. Assuring that summaries of training and experience are prepared for individuals assigned to the study.
5. Holding a pre-study meeting with CFSAN contract support personnel to discuss their functions and responsibilities during the conduct of the study.
6. Assigning a responsible individual to ensure that temperature and humidity in each animal room is recorded daily while the study is in progress.
7. All pertinent documentation regarding animals purchased from an outside source including purchase orders and delivery information.
8. Communicating on a regular basis with contractors who provide study support.
9. Maintaining records detailing the characterization of test and control articles.
10. Maintaining records indicating location of reserve samples.
11. Maintaining records concerning amount and distribution of test and control articles.
12. Maintaining results of analyses as part of the raw data for the study.

13. Maintaining records of homogeneity, concentration, and stability testing of test and control articles.
14. Ensuring that all experimental data, including observations of unanticipated responses of the test system, are properly and accurately recorded and verified.
15. Documenting and addressing unforeseen circumstances that may affect the quality and integrity of the nonclinical laboratory study.
16. Ensuring that test systems are as specified in the protocol.
17. Ensuring that all applicable GLP regulations are followed.
18. Preparing a final report, in accordance with CFSAN policies, and submitting it and all supporting data to the QA Unit for audit.
19. Making all necessary additions/corrections to the (draft) final report, in accordance with CFSAN policies, in a timely fashion.
20. Ensuring that all raw data, documentation, protocols, specimens, and final reports are transferred to the archives at the completion of the study.
21. Ensuring that the study is conducted in a safe manner and in accordance with the safety plan, safety procedures and safety requirements.

4.2.4 Veterinarian

The roles and responsibilities of CFSAN Veterinarians vary among CFSAN facilities. The following are basic duties of veterinarians (see IACUC and Animal Welfare Act for further guidance):
The veterinarian helps to ensure the following:

1. That adequate veterinary care is provided for animals used in research.
2. The health of laboratory animals used in studies and therefore, the quality and integrity of research conducted by CFSAN.

Responsibilities are performed to a standard that complies with regulations for proper animal care, including the following (see IACUC and Animal Welfare Act for further guidance):

1. Serves as a clearing place for the ordering or all animals used in the research facility. Acclimates all animals obtained from approved outside vendors prior to use in laboratory studies.
2. Quarantines all animals obtained from non-approved vendors prior to use in laboratory studies.
3. Receives animals when delivered to the MOD 1 facility. Designates alternate to act when veterinarian is not available.
4. Documents the receipt, health status, housing, care, and feeding of research animals during the acclimation period; see Good Laboratory Practice OECD Principles and Guidance for Compliance Monitoring [C(97)114/Final], 2006.
5. Provides records of receipt, health certification, and release of animals to study director at the end of the acclimation period.
6. Provides, upon request by the study director, consultation and all veterinary care to animals on study, including oversight of surgical procedures and appropriate euthanasia procedures.
7. Establishes approved Standard Operating Procedures (SOPs) as necessary for receipt, housing, care, and feeding of animals while they are under control of the CFSAN veterinarian.

8. Serves as a member of the CFSAN Institutional Animal Care and Use Committee (IACUC).
9. Provides training for animal care to all CFSAN employees and contractors in MOD 1.

Supporting information that will assist in fulfilling these requirements are:

- *Office of Laboratory Animal Welfare (OLAW) guidance*
- *Animal Welfare Act (AWA) www.nal.usda.gov/awic/legislat/usdaleg1.htm*
- The *Guide for the Care and Use of Laboratory Animals* guidance
- *www.aaalac.org/*

4.2.5 FDA Facilities Operations and Engineering Management

The Office of Real Property Services enhances the quality and integrity of the laboratory work conducted at CFSAN by carrying out the responsibilities listed below.

1. Serves as project oversight on all contracts whose obligations are to provide all aspects of building maintenance for systems and equipment relating to laboratory operations. This includes, but is not limited to, room and fume hood airflow, cold box and structural maintenance (walls, ceilings, floors), water, gas, and electrical services.
2. Provides guidance for the maintenance of all CFSAN-installed equipment. This includes offering technical assistance, making recommendations, and preparing requisitions necessary to contract for required services.
3. Provides assistance and recommendations on space utilization, assists in relocations, maintains air quality and air flow, temperature, and humidity for the testing facility.
4. Provides a mechanism for the control of vermin.

4.2.6 Warehouse/Storeroom Services Contractors

The Warehouse/Storeroom Services Contractor enhances the quality and integrity of the laboratory work conducted at CFSAN by carrying out the responsibilities listed below.

1. Receives and distributes laboratory and other supplies ordered for use.
2. Operates and maintains the FDA Scientific Supply Store.
3. Arranges for the shipment of appropriately packaged items, with the possible exceptions of radioactive materials and select agents and toxins, to their destination via GSA contract-approved transportation company or courier service.
4. Delivers gas cylinders and picks up empty gas cylinders upon request of laboratory personnel.
5. Provides pickup, processing, and transportation of medical waste to a centralized location for disposal.
6. Receives and stores equipment and supplies for use in the environmentally controlled Animal Facility that uses the supply/return corridor system at the MOD 1 facility.

4.2.7 Institutional Animal Care and Use Committee

The Institutional Animal Care and Use Committee (IACUC) enhances the quality and integrity of the laboratory work conducted at CFSAN by carrying out the responsibilities listed below, i.e., to ensure that the animals utilized in CFSAN research are humanely treated with minimization of pain and discomfort. As agreed to by AAALAC, the Dauphin Island and Moffett Facilities are inspected once a year when animals are on study. IACUC primary responsibilities are as follows (see Animal Welfare Act for further guidance):

1. Reviews CFSAN's animal research program at least once every 6 months using the *Guide for the Care and Use of Laboratory Animals* as a basis and to prepare reports of the status for the Institutional Official.
2. Inspects all animal facilities including animal study areas at least once every 6 months using the *Guide for the Care and Use of Laboratory Animals* as a guide and to prepare reports of the status for the Institutional Official. The Dauphin Island facility and Moffett Center Facility are inspected annually during a time when animals are on study.
3. Prepares reports of IACUC evaluations and submits the reports to the Institutional Official.
4. Reviews and investigates concerns involving the care and use of animals at CFSAN's research facilities resulting from public complaints or from reports of noncompliance received from facility personnel.
5. Makes recommendations to the Institutional Official regarding any aspect of CFSAN's Animal Program, animal facilities or personnel training.
6. Reviews and approves proposed activities related to the care and use of animals included in the protocol, protocol amendments, and standard operating procedures.
7. Suspends any activity involving animals, when necessary, if approved procedures are not followed.
8. Approves changes in study personnel involved in animal studies.

Supporting information that will assist in fulfilling these requirements is:

- *IACUC SOPs in eRoom*
- *www.aaalac.org/*
- *Public Health Service Policy on Humane Care and Use of Laboratory Animals*
- *Institutional Animal Care and Use Handbook*
- *Institutional Administrator's Manual for Laboratory Animal Care and Use*
- *Office of Laboratory Animal Welfare (OLAW) guidance*
- *Animal Welfare Act (AWA) www.nal.usda.gov/awic/legislat/usdaleg1.htm*

4.2.8 Animal Husbandry Contractor

The Animal Husbandry Contractor enhances the quality and integrity of animal studies conducted at CFSAN by carrying out the responsibilities listed below.

1. Provides all personnel necessary to perform animal husbandry services.
2. Provides technical support to the Veterinarian in acclimation services and procedures.
3. Performs daily observations to assess condition of animals housed in the environmentally controlled Animal Facility that uses the supply/return corridor system.
4. Monitors and records the environmental condition (temperature, humidity, directional air flow) of all active animal rooms and support areas.
5. Sanitizes and prepares the receiving dock to receive animal shipments into the facility and verifies accompanying documents.
6. Provides sufficient personnel to ensure that fresh feed and water are available to laboratory animals.
7. Operates tunnel and rack washers to provide clean cages, water bottles, litter pans, etc., in support of animal studies.
8. Provides support for technical procedures upon request of the study director.
9. Decontaminates, sanitizes, and maintains all animal rooms and environmentally controlled facilities that use supply/return corridor system passageways in a manner that ensures proper environments for conducting animal studies and that meet applicable procedures at the facility.
10. Develops and maintains IACUC-approved SOPs outlining the duties for areas covered by the Animal Husbandry Services Contract.
11. Participates in pre-study meetings which require interaction with other contract and government study personnel.

4.2.9 Glassware Contractor

The glassware contractor enhances the quality and integrity of the laboratory work conducted at CFSAN by carrying out the responsibilities listed below. These activities may vary among CFSAN facilities.

1. Maintains a central facility for the cleaning and storage of laboratory glassware.
2. Provides a mechanism for the ordering of specialized or new standard laboratory glassware.
3. Provides delivery of clean glassware and the pickup of dirty glassware.
4. Provides the storage, handling, and distribution of sterile laboratory glassware.

4.2.10 Media Services Contractors

The media services contractors enhance the quality and integrity of the laboratory work conducted at CFSAN by carrying out the responsibilities listed below.

1. Prepare and distribute sterile culture media.
2. Prepare and distribute selected buffers and saline solutions.

4.2.11 Safety Office

The Safety Office ensures that all laboratory work conducted at CFSAN is performed in compliance with all applicable occupational safety and health and environmental management regulations, standards, and CFSAN policies.

***Supporting information can be found at the CFSAN Safety Office intranet site*:**

http://inside.fda.gov:9003/CFSAN/OfficeofManagementSystems/ucm040820.html

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4.3 Personnel

Study Director

In consultation with Senior Management, the study director is influential in:

1. Determining adequate staffing levels and recruiting an adequate number of qualified individuals.
2. Justifying and filling position postings.
3. Reviewing applications and resumes.
4. Scheduling and overseeing the interview process.
5. Supporting the candidate selection process.
6. Scheduling new employees for appropriate training per their assigned responsibilities.
7. Overseeing the management of training, competencies, and evaluations.

4.3.1 Qualifications and Position Descriptions

Management (immediate supervisor and/or Office Director) shall ensure that personnel involved in the conduct of a study shall be qualified for their assigned duties. Management shall also ensure that a current position description for each individual engaged in, or supervising the conduct of, a nonclinical laboratory study is maintained in an organized manner and readily available upon request.

- Personnel performing critical tasks are qualified based on appropriate education, training, and experience.
- Position descriptions delineate the duties of the position.
- Position descriptions define appropriate qualifications, such as education, training, and experience, for each position.

The following information discussing qualifications and position descriptions is from 21 CFR 58.

- Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions.
- Each testing facility shall maintain a current summary of training and experience and a job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study.
- There shall be a sufficient number of personnel for the timely and proper conduct of the

study according to the protocol.

- Personnel shall take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems.
- Personnel engaged in a nonclinical laboratory study shall wear clothing appropriate for the duties they perform. Such clothing shall be changed as often as necessary to prevent microbiological, radiological, or chemical contamination of test systems and test and control articles.
- Any individual found at any time to have an illness that may adversely affect the quality and integrity of the nonclinical laboratory study shall be excluded from direct contact with test systems, test and control articles, and any other operation or function that may adversely affect the study, until the condition is corrected. All personnel shall be instructed to report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on a nonclinical laboratory study.

Supporting information that will assist in fulfilling these requirements is:

- *Staff Manual Guide 2020, Section 2, Resource Management*

4.4 Project Planning, Protocols, Procedures, and Conduct of GLP Studies

4.4.1 Project Planning

All CFSAN research projects that involve FDA personnel are to be posted in the CFSAN Automated Research Tracking System (CARTS) via the CFSAN Intranet. CARTS provides a mechanism for approval of projects by CFSAN management, as well as the sharing of information and tracking of progress on research and activities being conducted in CFSAN.

Activities conducted as a GLP study or as part of a GLP study are to be planned and conducted according to Good Laboratory Practices as described in 21 CFR part 58 and current CFSAN laboratory policies and procedures. Each nonclinical GLP study shall have an approved written protocol as described in section B of 21 CFR 58.120. The testing facility shall also have standard operating procedures as described in 21 CFR 58.81 and the study shall be conducted in accordance with 21 CFR 58.130 and CFSAN policies and procedures.

Procedures for planning and conducting research projects should include:

- Review of the relevant literature
- Determination of overall objectives
- Development of the experimental approach
- Determination of resource needs, including equipment, supplies, personnel, and budget
- Approval by management for conducting work with adequate and available resources
- Preliminary experimentation to develop protocols (if necessary)
- Determination of critical control points (areas) to monitor and ensure quality

- Documentation of raw data in an official laboratory notebook or similar record
- Completion of all necessary forms related to submission of the protocol for sign-off/approval
- Development of safety procedures and plans, including waste disposal

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Supporting information that will assist in fulfilling these requirements is:

- *http://fdswa090.fda.gov:81/qa/qa.htm*

4.4.2 Protocols

The study director/principal investigator (project lead) shall prepare appropriate protocol form (e.g., FDA form 3244b, ASP01, etc.), which have been designed to meet the GLP section related to Protocols (21 CFR 58.120). Protocols shall be reviewed as follows:

- Protocols for studies involving in the use of animals shall be reviewed by the Institutional Animal Care and Use Committee (IACUC) to ensure that animals utilized in CFSAN research are humanely treated with minimization of pain and discomfort.
- All protocols will be reviewed by the Safety Office.
- Protocols are reviewed by management and the QA Unit to ensure that they conform to GLP regulations and this Manual.
- All protocols using select agents and toxins will be reviewed by the site-specific Responsible Official or Alternate Responsible Official.
- All protocols using radioisotopes will be reviewed by the Radiation Safety/Protection Officer.

Projects/protocols meeting appropriate criteria will be signed and dated by the QA Unit; Protocols not meeting specific criteria will be returned to the study director/principal investigator (project lead), with comments for correction. The study director/principal investigator (project lead) shall review the comments, make necessary corrections, and resubmit the revised protocol to management, the QA Unit, IACUC, and the Safety Office for review. Protocols that have been signed and dated by the QA Unit are returned to the study director(s)/principal investigator(s) (project lead(s)) to begin their research. Protocols are to be retained with the study records. Please see SOP 3244b, *Initiation and Submission of CFSAN Project Approval Form 3244b.*

Modifications to approved study protocols must be made promptly by the study director using the CFSAN — Protocol Amendment form (FDA 3244a). Protocol Amendments must be submitted to the QA Unit in a timely manner. Additionally, amendments to the protocol that involve changes or additions to animal procedures must be approved by IACUC prior to being submitted to the QA Unit. Significant changes to the protocol that deviate from the approved safety plan, procedure, or protocol; change or modify the test article; or otherwise increase the nature of the hazard must be approved in advance by the Safety Office and Responsible Official/Alternate Responsible Official (if applicable).

The following information regarding protocols is from 21 CFR 58.120.

1. Each study shall have an approved written protocol that clearly indicates the objectives and all methods for the conduct of the study. The protocol shall contain, as applicable, the following information:
    a. A descriptive title and statement of the purpose of the study. Identification of the test and control articles by name, chemical abstract number, or code number.
    b. The name of the sponsor and the name and address of the testing facility at which the study is being conducted.
    c. The number, body weight range, sex, source of supply, species, strain, substrain, and age of the test system.
    d. The procedure for identification of the test system.
    e. A description of the experimental design, including the methods for control of bias.
    f. A description and/or identification of the diet used in the study, as well as solvents, emulsifiers, and/or other materials used to solubilize or suspend the test or control articles before mixing with the carrier. The description shall include specifications for acceptable levels of contaminants that are reasonably expected to be present in the dietary materials and are known to be capable of interfering with the purpose or conduct of the study if present at levels greater than established by the specifications.
    g. Each dosage level, expressed in milligrams per kilogram of body weight.
    h. The type and frequency of tests, analyses, and measurements to be made.
    i. The records to be maintained.
    j. The date of approval of the protocol by the sponsor and the dated signature of the study director.
    k. A statement of the proposed statistical methods to be used.

2. All changes in, or revisions of, an approved protocol and the reasons therefore shall be documented, signed by the study director/ principal investigator (project lead), and dated; for animal studies, signed and dated by the IACUC Chairperson and maintained with the protocol.

CFSAN Protocol Form Guidance

	GLP	Non-GLP
Studies involving animals	Form ASP01 and CARTS	Form ASP01 and CARTS
Studies not involving animals	FDA Form 3244b and CARTS	FDA Form 3244b and CARTS

Supporting information that will assist in fulfilling these requirements is:

- SOP 3244b, *Initiation and Submission of CFSAN Project Approval Form 3244b.*
- FDA Form 3244b, *CFSAN Project Approval Form*
- Form ASP01, *Animal Study Protocol*
- *42 CFR part 73 (HHS), the select agent regulations*
- *7 CFR part 331, Agricultural Bioterrorism Protection Act.*
- *9 CFR part 121, Possession, Use and Transfer of Biological Agents and Toxins.*
- *MOD-1 Select Agent Registration.*

4.4.3 Standard Operating Procedures (SOPs)

Standard operating procedures describe the way specific operations and methods are to be performed. These may include sampling operations, sample preparation, calibrations, measurement procedures, and any operation that is done on a repetitive basis. Peer-review of all methodology is a minimum requirement to ensure understandability and to enhance continuity of a measurement process, as well as to receive the benefit of technical feedback.

Laboratories involved in the conduct of a GLP laboratory study must prepare SOPs as required by the Good Laboratory Practice (GLP) Regulations, 21 CFR part 58 and in accordance with CFSAN policies. SOPs shall be written and approved by authorized individuals. These SOPs help insure the quality and integrity of the data generated during the course of the study. All SOPs developed for the care and use of laboratory animals must be provided with a protocol and be approved by IACUC during the protocol approval process. A historical file of SOPs and all revisions shall be maintained.
SOPs shall be:

- readily available to study personnel
- prepared by authorized personnel (e.g., IACUC) when involving the care of live animals
- developed for routine or repetitive laboratory tasks, as necessary
- maintained, filed, and distributed in such a manner that all necessary personnel have access

The following information regarding SOPs is taken from 21 CFR 58.81

1. A testing facility shall have standard operating procedures in writing setting forth nonclinical laboratory study methods that management is satisfied are adequate to ensure the quality and integrity of the data generated in the course of a study. All deviations in a study from SOPs shall be authorized by the study director and shall be documented in the raw data. Significant changes in established standard operating procedures shall be properly authorized in writing by management.

2. SOPs shall be established for, but not limited to, the following:
   a. Animal room preparation.
   b. Animal care.
   c. Receipt, identification, storage, handling, mixing, and method of sampling of the test and control articles.

d. Test system observations.
e. Laboratory tests.
f. Handling of animals found moribund or dead during study.
g. Necropsy of animals or postmortem examination of animals.
h. Collection and identification of specimens.
i. Histopathology.
j. Data handling, storage, archiving, and retrieval.
k. Maintenance and calibration of equipment.
l. Transfer, proper placement, and identification of animals.

3. Each laboratory area shall have immediately available laboratory manuals and SOPs relative to the laboratory procedures being performed. Published literature may be used as a supplement to SOPs.

4. A historical file of SOPs and all revisions thereof, including the dates of such revisions, shall be maintained.

4.4.4 Conduct of Studies

GLP studies conducted in CFSAN laboratories or conducted, in whole or in part, for CFSAN shall comply with 21 CFR 58.130 "Conduct of a nonclinical laboratory study" presented below. Such GLP studies shall be planned and conducted according to current CFSAN laboratory guidelines and in concurrence with quality standards presented in this manual. All contract and grant work at CFSAN laboratories conducted as part of a GLP study is to be planned and conducted according to GLP guidelines and the consulting laboratory, contractor, or grantee is to be notified that the service it is providing is part of a GLP laboratory study (21 CFR 58.10).

It is the responsibility of all individuals involved in the conduct of a study to ensure that all data are recorded appropriately and that corrections to recorded data are made appropriately. Additional responsibilities related to the conduct and documentation of studies are presented below.

The study director/principal investigator (project lead) shall:

- Ensure that procedures indicated in the approved protocol are followed by study personnel
- Ensure that appropriate documentation is maintained to support the results of the research conducted

Management shall:

- Review the progress of research conducted in their area on a periodic basis

Laboratory personnel shall:

- Take necessary personal sanitation and health precautions designed to avoid contamination of test and control articles and test systems
- Wear clothing and other personal protective equipment appropriate for the duties they perform. Such clothing and equipment shall be changed as often as necessary to prevent

microbiological, radiological, or chemical contamination.

- Report to their immediate supervisors any health or medical conditions that may reasonably be considered to have an adverse effect on the study

The following information regarding the conduct of a GLP laboratory study, from 21 CFR 58.130, is being presented for the convenience of the reader.

1. The nonclinical laboratory study shall be conducted in accordance with the protocol.
2. The test systems shall be monitored in conformity with the protocol.
3. Specimens shall be identified by test system, study, nature, and date of collection. This information shall be located on the specimen container or shall accompany the specimen in a manner that precludes error in the recording and storage of data.
4. Records of gross findings for a specimen from postmortem observations should be available to a pathologist when examining that specimen histopathologically.
5. All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in indelible ink. All data entries shall be dated on the date of entry and signed or initialed by the person entering the data. Any change in entries shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change. In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input. Any change in automated data entries shall not obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.

Ethics

To best serve customers, stakeholders, and employees, an organization's managers and staff need to be free of undue internal and external pressures that may adversely affect the quality of their work. Ethics standards promote and strengthen confidence in the integrity of the organization. CFSAN managers and supervisors ensure that federal, departmental, and FDA ethical standards are understood and followed by employees.

Supporting information that will assist in fulfilling these requirements is:

- *"FDA Ethics Program"*
  http://inside.fda.gov:9003/EmployeeResources/Ethics/FDAEthicsProgram/default.htm

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Confidentiality

To serve its customers, an organization protects information from inappropriate release or misuse, while maintaining appropriate transparency in their operations. CFSAN managers and supervisors shall strive to ensure that information disclosure, liabilities, responsibilities, and procedures are understood and followed by employees.

Supporting information that will assist in fulfilling these requirements is:

- *FDA SMG 2280.10, Protection of Non-Public Information http://inside.fda.gov:9003/PolicyProcedures/StaffManualGuide/VolumeIIIGeneralAdministration/ucm007444.html*
- *FDA/CFSAN Freedom of Information http://www.fda.gov/RegulatoryInformation/foi/default.htm*

4.5 Facilities

4.5.1 General

Each testing facility shall be of suitable size and construction to facilitate the proper conduct of nonclinical laboratory studies. It shall be designed so that there is a degree of separation that will prevent any function or activity from having an adverse effect on the study.

4.5.2 Animal Care Facilities

1. A testing facility shall have a sufficient number of animal rooms or areas, as needed, to ensure proper (1) separation of species or test systems, (2) isolation of individual projects, and (3) routine or specialized housing of animals.

2. A testing facility shall have a number of animal rooms or areas separate from those described in the previous paragraph to ensure isolation of studies being done with test systems or test and control articles known to be biohazardous, including volatile substances, aerosols, radioactive materials, and infectious agents.

3. Separate areas shall be provided, as appropriate, for the diagnosis, treatment, and control of laboratory animal diseases. These areas shall provide effective isolation for the housing of animals either known or suspected of being diseased, or of being carriers of disease, from other animals.

4. When animals are housed, facilities shall exist for the collection and disposal of all animal waste and refuse or for safe sanitary storage of waste before removal from the testing facility. Disposal facilities shall be so provided and operated as to minimize vermin infestation, odors, disease hazards, and environmental contamination.

4.5.3 Animal Supply Facilities (from 21 CFR 58.45)

There shall be storage areas, as needed, for feed, bedding, supplies, and equipment. Storage areas for feed and bedding shall be separated from areas housing the test systems and shall be protected against infestation or contamination. Perishable supplies shall be preserved by appropriate means.

4.5.4 Test and Control Article Facilities (from 21 CFR 58.47)

As necessary to prevent contamination or mix-ups, there shall be separate areas for:

1. Receipt and storage of the test and control articles.
2. Mixing of the test and control articles with a carrier, e.g., feed.
3. Storage of the test and control article mixtures.
4. Storage areas for the test and/or control article, and test and control mixtures shall be separate from areas housing the test systems and shall be adequate to preserve the identity, strength, purity, and stability of the articles and mixtures.

4.5.5 Laboratory Operation Areas

Separate laboratory space shall be provided, as needed, for the performance of the routine and specialized procedures required by nonclinical laboratory studies.

4.5.6 Archiving Specimens and Data

Space shall be provided for archives, limited to access by authorized personnel only, for the storage and retrieval of all raw data and specimens from completed studies.

4.5.7 Laboratory Housekeeping

CFSAN laboratories shall be maintained in a clean and orderly fashion to help ensure the quality and integrity of the data generated. Specific procedures necessary to maintain laboratory areas shall be developed and implemented.
Responsibilities are presented below:

Laboratory personnel

Laboratory personnel shall be held accountable for maintaining a neat, clean and uncluttered work area. This shall include taking steps to ensure that benches, cabinets, ceilings, walls and floors are kept clean and free of clutter, and that any unused or nonfunctional equipment is promptly and properly stored and/or permanently removed.

Laboratory supervisors

Supervisors shall ensure that personnel properly maintain neat and clean working areas. This shall include taking steps to ensure that benches, cabinets, ceiling, walls and floors are kept clean and free of clutter and that any unused or nonfunctional equipment is promptly and properly stored and/or permanently removed. Supervisors are responsible for ensuring that any deficiencies are corrected.

Study directors

All study directors shall ensure that all units involved in nonclinical laboratory studies have proper housekeeping procedures to help ensure the quality and integrity of study data. Study directors will discuss any deficiencies with unit management.

Supporting information that will assist in fulfilling these requirements is:

- *Material Safety Data Sheets (MSDS)*

4.6 Materials

4.6.1 Reagents and Solutions

Reagents, solutions, chemicals, and media shall be treated as follows:

1. All reagents and solutions in the laboratory areas shall be tracked/managed to include date received/opened/prepared, labeled to indicate identity, titer or concentration, storage requirements, and expiration date.

2. Deteriorated or outdated reagents and solutions shall not be used and shall be properly disposed of in accordance with standard operating procedures while observing all safety precautions.

3. Purchased chemicals, media and reagents should be received and tracked according to the Materials Management SOP.

4. Solutions and other reagents prepared in the laboratory should also be labeled to indicate date of preparation and the preparer's initials. Other information that may be pertinent should also be indicated on the label.

5. Reagents and solutions that contain hazardous components and require special protective measures while handling and storing them (e.g., need for protective equipment, use in hood, peroxide-forming compound) shall have an appropriate warning sticker affixed to each container.

Supporting information that will assist in fulfilling these requirements is:

- *Draft Materials Management Procedure*

4.6.2 Test and Control Article Characterization

Test and control articles shall be treated as follows:

1. The identity, strength, purity, and composition or other characteristics which will appropriately define the test or control article shall be determined for each batch and shall be documented. Methods of synthesis, fabrication, or derivation of the test and control articles shall be documented by the sponsor or the testing facility. In those cases where marketed products are used as control articles, such products will be characterized by their labeling.

2. The stability of each test or control article shall be determined by the testing facility or by the sponsor (if applicable), either: (1) Before study initiation, or (2) concomitantly according to written standard operating procedures, which provide for periodic analysis of each batch.

3. Each storage container for a test or control article shall be labeled by name, chemical abstract number or code number, batch number, expiration date, if any, and, where appropriate, storage conditions necessary to maintain the identity, strength, purity, and composition of the test or control article. Storage containers shall be assigned to a particular test article for the duration of the study.

4. For studies of more than 4 weeks duration, reserve samples from each batch of test and control articles shall be retained for as long as the quality of the material/preparation affords evaluation or for a period of not less than 5 years from the date of approval of the final report.

4.6.3 Test and Control Article Handling

Procedures shall be established, as described in 21 CFR 58.107, for a system of handling the test and control articles to ensure that:

1. There is proper storage.
2. Distribution is made in a manner designed to preclude the possibility of contamination, deterioration, or damage.
3. Proper identification is maintained throughout the distribution process.
4. The receipt and distribution of each batch is documented. Such documentation shall include the date and quantity of each batch distributed or returned.

4.6.4 Mixtures of Articles with Carriers

Tests by appropriate analytical methods shall be conducted:

- To determine the uniformity of the mixture and to determine, periodically, the concentration of the test or control article in the mixture.

- To determine the stability of the test and control articles in the mixture as required by the conditions of the study, either:
  a. Before study initiation, or
  b. Concomitantly according to written standard operating procedures which provide for periodic analysis of the test and control articles in the mixture.

The expiration date of the components of the test or control article carrier shall be clearly shown on the container. If more than one component has an expiration date, the earliest date shall be shown.

4.7 Test System

CFSAN recognizes that the term "test system" includes any animal, plant, or microorganism to which a test or control article is administered. This section focuses attention, however, on the subject matter that is presented in "Test Systems" as presented in 21 CFR 58.90.

4.7.1 Care of Laboratory Animals

Animals involved in nonclinical GLP laboratory studies must be housed, handled, and cared for in a manner that is consistent with the requirements of the Animal Welfare Act, the Public Health Service Guidelines, 21 CFR 58.90, and *Guide for the Care and Use of Laboratory Animals*. At MOD I, the animal husbandry services are provided by the Animal Husbandry Contractor, whose duties include maintaining an environment conducive to the humane treatment of animals involved in scientific research. Although animal care services are available from the contractor, a researcher if he/she wishes, may perform the animal care for his/her study provided that the standard operating procedures for the environmentally controlled Animal Facility that use supply/return corridor system are observed.

The following information regarding animal care is from 21 CFR 58.90:

1. There shall be IACUC-approved standard operating procedures (SOPs) for the housing, feeding, handling, and care of animals.
2. All newly received animals from outside sources shall be isolated and their health status shall be evaluated in accordance with acceptable veterinary medical practice.
3. At the initiation of a nonclinical laboratory study, animals shall be free of any disease or condition that might interfere with the purpose or conduct of the study. If, during the course of the study, the animals contract such a disease or condition, the diseased animals shall be isolated, if necessary. These animals may be treated for disease or signs of disease provided that such treatment does not interfere with the study. The diagnosis, authorizations of treatment, description of treatment, and each date of treatment shall be documented and shall be retained.
4. Warm-blooded animals, excluding suckling rodents, used in laboratory procedures that require manipulations and observations over an extended period of time or in studies that require the animals to be removed from and returned to their home cages for any reason (e.g., cage cleaning, treatment, etc.), shall receive appropriate identification. All information needed to specifically identify each animal within an animal-housing unit shall appear on the outside of that unit.
5. Animals of different species shall be housed in separate rooms when necessary. Animals of the same species, but used in different studies, should not ordinarily be housed in the same room when inadvertent exposure to control or test articles or animal mixup could affect the outcome of either study. If such mixed housing is necessary, adequate differentiation by space and identification shall be made.
6. Animal cages, racks, and accessory equipment shall be cleaned and sanitized at appropriate intervals.
7. Feed and water used for the animals shall be analyzed periodically to ensure that contaminants known to be capable of interfering with the study and reasonably expected to be present in such feed or water are not present at levels above those specified in the protocol. Documentation of such analyses shall be maintained as raw data.

8. Bedding used in animal cages or pens shall not interfere with the purpose or conduct of the study and shall be changed as often as necessary to keep the animals dry and clean. Bedding and bedding changes are in accordance with the *Guide for the Care and Use of Laboratory Animals*.
9. If any pest control materials are used, such use shall be documented. Cleaning and pest control materials that interfere with the study shall not be used.

4.8 Equipment

This policy provides direction for processes and procedures to effectively manage CFSAN instruments, equipment, and computer systems. The term equipment is used to refer to all equipment, instruments, measuring devices, and computer systems used in evaluating and or performing research. Each research unit shall ensure that appropriate validation, calibration, maintenance, and monitoring of equipment conform to applicable regulatory requirements, laws, and standards.

The following information regarding maintenance and calibration of equipment is from 21 CFR 58.63:

(a) Equipment shall be adequately inspected, cleaned, and maintained. Equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated and/or standardized.

(b) The written standard operating procedures required under Sec. 58.81(b)(11) shall set forth in sufficient detail the methods, materials, and schedules to be used in the routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment, and shall specify, when appropriate, remedial action to be taken in the event of failure or malfunction of equipment. The written standard operating procedures shall designate the person responsible for the performance of each operation.

(c) Written records shall be maintained of all inspection, maintenance, testing, calibrating and/or standardizing operations. These records, containing the date of the operation, shall describe whether the maintenance operations were routine and followed the written standard operating procedures. Written records shall be kept of nonroutine repairs performed on equipment as a result of failure and malfunction. Such records shall document the nature of the defect, how and when the defect was discovered, and any remedial action taken in response to the defect.

4.8.1 Responsibilities

Study director/principal investigator (project lead) is responsible for the following:

a. Maintaining a list of equipment used with a given GLP study.
b . Removal of equipment from service when not functioning appropriately or when calibration or maintenance has not been performed (i.e., placement of sign on equipment indicating that it is out of service).
c. Contacting appropriate group for assessment and/or repair when equipment is not functioning appropriately.

d. Developing and maintaining schedule and records for the maintenance and calibration of equipment.
e. Performing tasks to monitor equipment validation, calibrations, and maintenance.
f. Maintaining control of equipment user manuals.
g. Reviewing data and records related to equipment.

Additional information regarding equipment design, maintenance, and calibration can be found in the Equipment Management SMG.

Supporting information *that will assist in fulfilling these requirements is* :

- *Draft Equipment Management Procedure*

4.9 Training, Education, and Experience

Employee training is an integral part of the process necessary for best laboratory practices. Training should be conducted in a consistent manner. New employees must be adequately trained with respect to the general policies and processes of quality assurance, as well as be trained, as necessary, for their specific position duties and responsibilities.

A training and experience form is required for each technique an investigator will be performing on an animal. A standard training and experience form is required for each person on an animal protocol that is maintained with the approved protocol. Annual Select Agent Training is required for everyone working with select agents.

Management (immediate supervisor and/or Office Director) shall ensure that each individual engaged in the conduct of, or responsible for, the supervision of a laboratory study shall have education, training, and experience, or a combination thereof, to enable these individuals to properly perform the assigned duties. Training and education includes, but is not limited to the following:

- Quality assurance training consistent with duties and responsibilities
- Policies contained in this Manual
- Training in best laboratory practices and procedures needed to do relevant laboratory work
- Safety training consistent with duties and responsibilities

Methods of demonstrating competency include:

- Discussions/reviews with employee
- Performance/direct observations
- Written and/or oral examination

Management (immediate supervisor and/or Office Director) shall ensure that a current summary of training and experience for each individual engaged in or supervising the conduct of a laboratory study is maintained. Training and experience can be documented by curriculum vitae, resumes, training certificates, etc.

Staff College shall be responsible for maintaining records of training activities it has provided (DHHS sponsored courses are captured in the Learning Management System) and names of those who attended those courses. For non-DHHS courses, individual employees shall be responsible for making copies of documentation of training (e.g., training certificates) and providing this information to designated individual(s), usually the immediate supervisor. The immediate supervisor will maintain and ensure that these records are kept in an organized manner and are readily available upon request.

Supporting information that will assist in fulfilling these requirements is:

- *CFSAN Staff College* - *http://inside.fda.gov:9003/EmployeeResources/Training/StaffCollegeCFSAN/default.htm*

4.10 Documents and Records

4.10.1 Creation of Data and Records

Research data generated in or for CFSAN are the property of the FDA.

"*Official" Laboratory Notebooks*
Official laboratory notebooks are the preferred medium for recording laboratory data. However, other forms of documentation such as forms, diagrams, and electronic media, may replace or be used in conjunction with laboratory notebooks with appropriate cross-referencing. All electronic data outputs should have a system for documentation, cross-referencing, backup, and storage of the work (i.e., copying files to a shared drive, a second hard drive, or other optical or magnetic media).

The management of "official" laboratory notebooks is the responsibility of the Office Director or their designee. Each office will be responsible for procuring, distributing, and tracking the notebooks as described in the CFSAN staff manual guide titled "Use and Management of CFSAN Official Laboratory Notebooks."

A laboratory notebook assigned to an employee who is separating from the laboratory and/or the FDA must be turned in to the first line supervisor, who will be responsible for maintaining the notebook and other research information.

In accordance with 21 CFR 58.130 the following shall be followed:

All data generated during the conduct of a nonclinical laboratory study, except those that are generated by automated data collection systems, shall be recorded directly, promptly, and legibly in indelible ink.

- All data entries shall be dated on the date of entry and signed or initialed by the person entering the data.
- Any change in entries shall not obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of the change.
- In automated data collection systems, the individual responsible for direct data input shall be identified at the time of data input.
- Any change in automated data entries shall be made so as not to obscure the original entry, shall indicate the reason for change, shall be dated, and the responsible individual shall be identified.

4.10.2 Archiving of Data

CFSAN shall maintain a centralized archive for nonclinical laboratory studies. The archived laboratory records storage are managed by CFSAN's Records Management section. These archives shall:

1. Provide for orderly storage and expedient retrieval of raw data, documentation, protocols, specimens, and interim and final reports
2. Provide conditions of storage that minimize deterioration of the documents or specimens

Commercial archives may be used to provide a repository for appropriate material to be retained. Raw data and specimens may be retained elsewhere provided that the archives have specific reference to those other locations. CFSAN's archivist is responsible for the archives, and only authorized personnel shall enter the archives. See the reference the record retention schedule.

4.10.3 Retention of Records

Raw data, documentation, protocols, final reports, and specimens (except those specimens obtained from mutagenicity tests and wet specimens of blood, urine, feces, and biological fluids) generated as a result of a nonclinical laboratory study shall be retained for a period of not less than 5 years from the date of approval of the final report. However, samples of test or control articles, and specially prepared material, which are relatively fragile and differ markedly in stability and quality during storage, shall be retained only as long as the quality of the preparation affords evaluation.

The following documents shall also be retained for a period of not less than 5 years from the date of approval of the final report:

1. The master schedule sheet, copies of protocols, and records of quality assurance inspections, as required by 21 CFR 58.35(c), shall be maintained by the QA Unit as an easily accessible system of records.

2. Documentation of training and experience and position descriptions as required by 21 CFR 58.29(b) and described in section 4.10 of this manual (i.e., training, education and experience).

3. Records and reports of the maintenance and calibration and inspection of equipment as required by 21 CFR 58.63(b) and c), and described in section 4.9 of this manual (i.e., equipment).

4.10.4 Retrieval of Data and Records

Data, documentation, protocols, final reports, specimens, and records that have been archived by or for CFSAN may be retrieved from the archives by following the procedures for retrieval of records and data described in the CFSAN laboratory operations guidance documents.

Supporting information that will assist in fulfilling these requirements is:

- *Draft Good Laboratory Practices Study Data Archives*
- *FDA Record Control Schedule*
  http://inside.fda.gov:9003/it/RecordsManagement/RetentionInstructions/default.htm

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4.11 Project Reporting

Reports for projects are to be posted to the CARTS according to the currently accepted procedures and periodic progress reports should be prepared as requested by management.

A final report shall be prepared for all nonclinical laboratory studies conducted in compliance with 21 CFR 58 (GLP studies) and CFSAN policy. The final report, final report appendix, and amendment forms that are to be used for nonclinical laboratory studies have been designed to ensure compliance with the Good Laboratory Practice Regulations (21 CFR 58.185).

Preparation of the Final Report

A final report shall be prepared by the study director at the conclusion of each study providing the information specified in form FDA 3224, *Nonclinical Laboratory Study Final Report.* It is the responsibility of the study director/principal investigator (project lead) to ensure accuracy and completeness of the study report and its compliance with 21 CFR 58. The final report shall be signed and dated by the study director and a member of the QA Unit.

Preparation of the Appendix to the Final Report

Appendices to the final report shall be prepared by the principal investigator (project lead) of the unit that provided the support for the study (i.e., Chemistry, Pathology, Mathematics, etc.). The principal investigator (project lead) shall use form FDA 3224b, *Nonclinical Laboratory Study Appendix to the Final Report*. The Appendix to the final report shall be signed and dated by the principal investigator(s) (project lead(s)) and submitted to the study director in charge of the study for which the support was provided.

Preparation of Final Report Amendments

Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible.

Any addition or correction made to the final report once it is signed by the study director must be done using form FDA 3224a, *Nonclinical Laboratory Study Amendment to the Final Report*. A responsible official in the QA Unit shall also sign this form.

QA Unit Review

The Quality Assurance Unit shall review the final report and audit the data generated to ensure that (a) the report is consistent with the approved protocol and SOPs; (b) changes made to the protocol and SOPs were authorized and documented; (c) the reported results accurately reflect the raw data. The QA Unit shall then prepare and sign a Quality Assurance Clearance Statement to be attached to the final report.

Supporting information that will assist in fulfilling these requirements is:

- *http://intranet.cfsan.fda.gov/*

4.12 Audits

Information regarding monitoring processes, conducting and/or participating in audits and inspections, as well as verifying data generated during the conduct of laboratory activity and handling of regulatory samples are critical elements of a quality system.

An organization undergoes audits and/or assessments to determine whether their quality system conforms to applicable requirements and is effectively implemented and maintained: audits evaluate the quality system. Actions taken based on audit results can enhance strengths and reduce weaknesses in an organization.

CFSAN participates in internal and external audits on a periodic basis. Internal audits are performed to measure strengths and weaknesses in actual performance against CFSAN procedures, methods, or applicable standards, including safety standards. External audits are performed to demonstrate to the inspection organization that CFSAN is in compliance with applicable rules, regulations, and guidelines. Internal audits will be conducted at planned intervals to evaluate whether the QS conforms to applicable requirements outlined in this document and are effectively implemented and maintained.

The QA Unit will be responsible for the following auditing activities (internal and external):

- Developing and documenting internal audit procedures

- Developing and documenting external inspection procedures
- Ensuring that managers responsible for the areas audited take timely action on resolving audit findings
- Ensuring that follow-up activities are completed, verified, and recorded.
- Ensuring that the audit reports are forwarded to senior management in a timely manner.

Supporting information that will assist in fulfilling these requirements is:

- *Draft Internal Audit Policy*
- *Draft CFSAN Internal Audit SOP*
- *Draft Management of External Inspections*

4.13 Corrective Action/Preventive Action

Corrective Actions
When quality-related problems and issues are identified, the organization resolves them and prevents them from recurring. Problems may be identified through data analysis, nonconformity reports, audit and proficiency reports, management review meetings, complaints, customer satisfaction queries, or internal feedback. Corrective action includes evaluation of the significance of the problem and the impact on operating costs, error costs, product fitness, and customer satisfaction.

- CFSAN managers shall ensure that documented procedures are maintained to investigate root causes of nonconformances and complaints, to implement effective corrective action to prevent recurrence, and to prepare summaries for management review.
- CFSAN managers shall ensure that corrective action is taken in reaction to a significant risk to quality or a departure from an established procedure.

Preventive Actions
Quality is most efficiently achieved by preventing problems from occurring rather than detecting problems afterwards. Prevention is based on quality and process planning, process control, training, and other aspects of the quality system. Results of data analysis, changes in organization, or changes in the operating environment may suggest potential problems. The need for preventive actions is based upon the significance and impact of the potential problem.

- CFSAN managers shall ensure CFSAN establish and maintain documented procedures to identify the root causes of potential quality problems, to select the necessary deterrents so that the problem does not occur, and to prepare summaries for management review.
- The CFSAN managers shall ensure preventive action procedures are used proactively when significant risk of possible problems is identified.

Supporting information that will assist in fulfilling these requirements is:

- *Draft Corrective/Preventive Action Procedure*

4.14 Continual Improvement

A quality system is an integral part of a dynamic, growing organization. CFSAN managers shall continually improve the quality system. Improvements may be reactive (corrective) or proactive (preventive).

- CFSAN QMS uses the tools outlined in this Quality Manual – the quality policy and objectives, process and product measurement, data analysis, feedback, audit results, corrective and preventive actions, and management reviews – to facilitate continual improvement. Continual improvement encompasses both incremental improvements within the existing processes and major changes in process redesign.
- CFSAN managers shall ensure that preventive action procedures are used proactively when significant risks of possible problems are identified.

Documenting Complaints

CFSAN shall maintain a process for documenting complaints related to issues that may impact QC/QA, as well as complaints initiated from the research staff regarding quality issues.

Supporting information that will assist in fulfilling these requirements is:

- *Anonymous CFSAN Employee Suggestions (ACES) http://fdswa090.fda.gov/aces/*

4.14.1 Quality Monitoring

Quality monitors are specific performance measurements or indicators designed to monitor one or more processes during a defined time and are useful for evaluating progress.

- In accordance with the scope and objectives set by responsible officials, the QA Unit identifies quality indicators to monitor the performance of selected processes. The QA Unit maintains processes and schedules for collection and evaluation of quality indicator data.
- Quality monitors are defined for short-term and long-term audits of processes.
- Quality monitors are adopted as needed based on the current events of CFSAN to monitor deviations and nonconformances.
- Quality monitors can be defined by various management groups to evaluate the effectiveness of CFSAN's policies, processes and procedures.

4.15 Studies Performed under Grants and Contracts

Contracted laboratory work conducted in association with a GLP study must conform to the CFSAN quality standard described in this manual and with 21 CFR 58.10, as follows: "When a

sponsor conducting a nonclinical laboratory study intended to be submitted to or reviewed by the Food and Drug Administration utilizes the services of a consulting laboratory, contractor, or grantee to perform an analysis or other service, it shall notify the consulting laboratory, contractor, or grantee that the service is part of a nonclinical laboratory study that must be conducted in compliance with the provisions of this part" (21 CFR 58.10).

Supporting information that will assist in fulfilling these requirements is:

- *SMG 2610.1- Acquisition of Supplies and Services Under Contracts* *http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm162041.htm*
- *SMG 2150.2 – Grants Management – Grants and Cooperative Agreement* http://inside.fda.gov:9003/PolicyProcedures/StaffManualGuide/VolumeIIIGeneralAdministration/ucm007150.html

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5.0 Regulatory Samples

It is important to ensure that regulatory samples received by CFSAN are managed and processed according to FDA policies and procedures. In this respect, the Office of Regulatory Affairs (ORA) Laboratory Manual (at the website given below) offers useful guidance regarding the management of regulatory samples. The Table of Contents gives the titles of the procedures in each volume.

Volume I of the ORA Manual is the policy manual; Volume II, Section 1 contains the management template procedures, Volume II, Section 2 (which is mandatory) contains the technical procedures (method selection, traceability, assuring test results, etc). Volume III contains guidance procedures that are FDA-specific, such as sample handling, preparing analyst worksheet, research, statistics, etc.

If an analysis is based on a Compliance Program (CP) or assignment, field laboratories must additionally follow the requirements of the ORA Laboratory Manual. These requirements are mandatory for any type of analytical work, i.e., regulatory, consumer complaints, proficiency test samples, inter-laboratory confirmations. FDA field laboratories are also directed to follow the appropriate CP and CFSAN Field Assignments. CFSAN Compliance Programs can be accessed at the websites given below.

Supporting information that will assist in fulfilling these requirements is:

- *http://inside.fda.gov:9003/PolicyProcedures/Laboratories/ORA%20Laboratory%20Manual/default.htm*
- *http://www.cfsan.fda.gov/~comm/cp-toc.html*
- *http://inside.fda.gov:9003/ProgramsInitiatives/Food/FieldPrograms/ucm013763.html*

6.0 Good Clinical Practice

The Quality Assurance Program for GCP and Human Studies is currently being developed. Additional information on procedures to follow when performing a study involving a human subject is available at
http://inside.fda.gov:9003/CFSAN/OfficeoftheCenterDirector/ScienceResources/ucm030279.html

http://inside.fda.gov:9003/PolicyProcedures/StaffManualGuide/VolumeIOrganizationsandFunctions/ucm077138.html

7.0 References

21 CFR part 58 - Good Laboratory Practice for Nonclinical Laboratory Studies

Animal Welfare Act (AWA) www.nal.usda.gov/awic/

Quality Guidelines for Research (**ANSI/ASQ Z1.13-1999)**

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DC Singer, 2001, *A Laboratory Quality Handbook of Best Practices and Relevant Regulations*, ASQ Quality Press, Milwaukee, WI

FM Garfield, E Klesta and J Hirsch, 2000, *Quality Assurance Principles for Analytical Laboratories*, 3rd edition, AOAC International, Gaithersburg, MD (excerpted with permission of AOAC International).

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JD Cook, Guest Essay, *Good Laboratory Practice (GLP) Versus CLIA*, Baltimore, MD
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ORA Quality Manual, January 2007 version

R Westcott, 2005, *The Certified Manager of Quality/Organizational Excellence Handbook*, ASQ Quality Press, Milwaukee, WI

Staff Manual Guide (SMG) 2020: FDA Quality System Framework for Internal Activities
(http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm052570.htm)

JK Taylor, 1978, *Quality Assurance of Chemical Measurements*, Lewis Publishers, Chelsea, MI pp 177-186

Appendix

A. Organizational Chart

(http://www.fda.gov/AboutFDA/CentersOffices/OrganizationCharts/ucm135675.htm)

A. CFSAN Organizational Structure

See the CFSAN intranet for the most recent copy of the organizational chart.