COLLEGE of AMERICAN PATHOLOGISTS

February 2, 2015

Margaret A. Hamburg, MD
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket No. DA-2011-D-0360: FDA Draft Guidance Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

Dear Dr. Hamburg:

The College of American Pathologists (CAP) appreciates this opportunity to comment on the Food and Drug Administration (FDA) draft guidance entitled, *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*. The CAP, *celebrating 50 years as the gold standard in laboratory accreditation,* is a medical society serving more than 18,000 physician members and the global laboratory community. It is the world's largest association composed exclusively of board-certified pathologists and is the worldwide leader in laboratory quality assurance. The College advocates accountable, high-quality, and cost-effective patient care. The CAP Laboratory Accreditation Program (LAP) is responsible for accrediting more than 7,000 clinical laboratories worldwide. Our members have extensive expertise in providing and directing laboratory services and also serve as inspectors in the Centers for Medicare & Medicaid Services (CMS)-deemed CAP accreditation program.

The CAP also provides laboratories with a wide variety of proficiency testing programs and has the responsibility to evaluate the accuracy of test performance and interpretation in more than 23,000 laboratories worldwide. The program allows laboratories to evaluate their performance regularly and improve the accuracy of the patient results they provide. Through these programs, the CAP provides individual laboratories with unknown specimens for testing. The participants analyze the specimens and return the results to the CAP for evaluation. In turn, each participating laboratory receives a report of its performance as well as a report summarizing the results of all participating laboratories.

We appreciate your leadership in proposing a comprehensive framework for the regulation of LDTs; but as written we believe the guidance may stifle medical innovation, is too burdensome on laboratories, and may interfere with the delivery of potentially life-saving testing to patients.
The CAP has unique insights into the benefits and risks presented by LDTs and the many practical issues surrounding their regulation. As physician specialists in the diagnosis of disease, pathologists have a long track record of delivering high-quality services to patients through the practice of medicine. Pathologists therefore have a keen interest in ensuring that our ability to provide high-quality diagnostic services to patients and other physicians is not overly restricted. Furthermore, as a deemed accreditation agency, the CAP has had

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

oversight responsibilities in a variety of laboratory settings, from complex university medical centers to physician offices covering a complete array of disciplines and testing procedures available in today's laboratory.

THE CAP'S POSITION ON LDT OVERSIGHT

The CAP believes that any oversight framework imposed by the federal government must be appropriate to the way modern clinical laboratories provide patient testing. This includes being prudent in determining which LDTs are included in the proposed oversight. LDTs include a vast range of tests and test modifications that range from minor modifications of FDA-approved tests to proprietary tests that are performed in single laboratories using proprietary algorithms. This broad net includes some of the most innovative clinical testing being offered today that is critical to providing information to physicians caring for patients. In 2009, the CAP outlined and shared with the FDA its proposal for the rational oversight of LDTs. (See Appendix A). We continue to support our 2009 proposal, which contains the following features:

- Provides a tiered risk-based regulation that would focus oversight to the tests that currently have the least transparency and highest potential patient risk.
- Allows for evaluation of patient risk based on a laboratory's claims for the test and the potential for harm to patients of an incorrect or misinterpreted test.
- Provides for achievable and targeted FDA oversight of high-risk LDTs as we define these categories in our proposal.
- Provides assurance of both analytic and clinical validity of laboratory tests.
- Allows for continued CMS oversight of laboratory quality under Clinical Laboratory Improvements Amendments of 1988 (CLIA) for moderate- and low-risk LDTs as we define these categories in our proposal.
- Encourages coordination between the FDA and the CMS to avoid duplicative or unduly burdensome requirements on laboratories.
- Promotes innovation of new diagnostic and predictive tests.
- Protects the ability of pathologists to continue to bring lifesaving testing to patients through the practice of medicine.

We note several similarities between the CAP proposal and the FDA guidance. These include a focus on analytical and clinical validity, a three-tiered risk based approach to LDT categorization and oversight, enforcement discretion for LDTs identified as having low risk to patients, and FDA focus on those tests that pose a higher risk to patients. However, there are several critical differences between the CAP approach and the one in the FDA Draft Guidance. In particular, there are significant differences in how our proposal defines an LDT and the risk classification for LDTs. As such, we also differ in our view of the appropriate role of CLIA and the CMS within the regulatory process.

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

We offer comments on the following areas of the FDA Draft Guidance for LDT Oversight:

- Components of a Test and LDT Labeling Considerations
- Clinical Validity/Intended Use
- Categories for Continued Enforcement Discretion
- Process for Classification and Prioritization
- Quality Systems Regulations

Our comments on the notification and adverse reporting requirements will be provided in a separate letter.

COMPONENTS OF A TEST AND LDT LABELING CONSIDERATIONS

Components of a Test

A laboratory is considered to have developed a test if the test *procedure* or protocols were created by and implemented in that laboratory, irrespective of whether fundamental research underlying the test was developed elsewhere or reagents, equipment, or technology integral to the test was purchased, adopted, or licensed from any other entity.

LDTs are not restricted to any particular test methodology. LDTs may rely on biochemical, genetic, morphological, or other techniques. Examples of LDTs include genetic tests for breast cancer and tests for emergent and potentially fatal infectious diseases such as herpes encephalitis and H1N1 influenza.

The CAP believes an LDT must possess the following characteristics:

1. The test is performed by the clinical laboratory in which it was developed; and
2. The test has not previously been approved or cleared by the FDA as an in vitro diagnostic device.

An LDT may or may not employ analyte-specific reagents (ASR), research-use only reagents (RUO), or investigational use only (IUO) reagents; the type(s) of reagent(s) and device(s) employed should not affect whether a test is classified as an LDT. The CAP believes that use of RUO and IUO reagents, instruments, and systems as components of LDTs should be permissible in clinical diagnosis and patient management when laboratory personnel have validated the test. We assert that performance of LDTs can be safely assured through the CLIA certification, accreditation and inspection processes, proper assay validation, and ongoing proficiency testing. The laboratory directors of clinical laboratories which offer tests using RUO instruments, software, and reagents can and do recognize the potential problems and, through strict adherence to quality management and assay validation, establish a high degree of assurance of test quality.

Existing CLIA regulations, with which laboratories currently must comply, provide the necessary review for most laboratory tests incorporating ASRs, RUOs, and/or IUOs. Tests that include these components are validated by professional laboratory personnel through

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

existing regulatory processes, which address analytical and clinical validity and do not require further regulation based on the provenance of reagents.

We have also heard concerns from our members that as written the guidance would impact their ability to provide appropriate and critical testing for their patients. The FDA's definition of LDTs would prevent many innovative tests developed and used within health care systems from being available for patient care. Health care delivery has evolved overtime from single institution models to integrated multidiscipline health care models serving a patient population. These new models were developed to improve access and quality of care as well as ensure continuity of care and better health outcomes. The laboratories in many of these systems continue to operate collectively as a single laboratory when developing an LDT. We believe the FDA's definition would arbitrarily restrict these laboratories that have the same safeguards and controls as single laboratories from developing vital tests.

Therefore, we recommend the definition of a laboratory in the proposed FDA LDT definition be expanded to include health care systems under common ownership.

We believe that clarifying and potentially broadening the proposed FDA definition to include health care system would maximize patients' access to LDTs. LDTs developed in these systems continue to mitigate the level of risk to patients and exhibit the same characteristics as those developed in a single laboratory (ie, developed in small numbers, involved pathologist-clinician communications, used on patient population served).

LDT Labeling Considerations

We believe a standard disclosure statement should be included on the test report for any LDT and that analytic and clinical validity data should be made available upon request. Specifically, the CAP recommends the FDA allow laboratories to label an LDT with the following standardized statement:

- **"The [name of test] used to produce this report was developed and performance characteristics determined by Laboratory X.**
- **Analytical and clinical validity data are available upon request. "**

The FDA established the unique device identification system to adequately identify medical devices' intended use with the purpose of improving patient safety through better tracking and modernizing device post-market surveillance.[1]

However, the CAP does not believe that FDA should require laboratories to add Unique Device Identifiers (UDI) to an LDT label, as proposed under the draft FDA Guidance, for three reasons.

1. An LDT is not distributed like a medical device and is unique, easily identifiable, and traceable to the laboratory that develops and performs it. The vast majority of LDTs would be considered low-risk and therefore equivalent to Class I devices, which are

[1] 21 CFR 801.55.

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

exempt from the good manufacturing practices (GMP) requirements and the UDI requirements.

2. The CLIA regulations have requirements that allow for accurate, precise, and rapid test identification[2].
3. It may not be technologically feasible for laboratories to generate a number on each test due to the limitations of some laboratory information systems.

For these reasons, the CAP believes UDIs should not be required on any LDT labels.

CLINICAL VALIDITY/INTENDED USE

Pathologists, in their roles as laboratory directors under CLIA, are responsible for assuring that all the tests are clinically valid. Pathologists, physicians who practice laboratory medicine, determine the intended use for tests and provide test results to the treating clinician. For example, BRAF is a biomarker utilized for multiple purposes in melanoma, colon cancer, thyroid cancer, and other conditions. Although test results will influence treatment decisions, they are one of many factors considered when a clinician and a patient determine a patient's course of therapy.

For the vast majority of LDTs, the intended use is linked to the clinical claims of the tests (i.e. clinical validity). The CAP accredited laboratories that perform molecular testing are required by the CAP LAP program to demonstrate clinical validity for each LDT. We define clinical validity as a test's ability to detect or predict a disorder, identify a prognostic risk or other condition. The elements considered in the evaluation of clinical validity may include some or all of the following metrics:

- Clinical sensitivity (clinical detection rate for a given population of patients): the proportion of individuals with a disorder, prognostic risk, or condition that are detected by the test.

- Clinical specificity: the proportion of individuals without a disorder, prognostic risk, or condition that are excluded by the test.

- Reference limits: a value or range of values for a test that contribute to clinical decision-making. A reference interval, a type of reference value, is the range of test values expected for a designated population of individuals. This may be the central 95% interval of the distribution of values from individuals who are presumed to be

[2] (c) The test report must indicate the following:
(1) For positive patient identification, either the patient's name and identification number, or a unique patient identifier and identification number.
(2) The name and address of the laboratory location where the test was performed.
(3) The test report date.
(4) The test performed.
(5) Specimen source, when appropriate.
(6) The test result and, if applicable, the units of measurement or interpretation, or both.
(7) Any information regarding the condition and disposition of specimens that do not meet the laboratory's criteria for acceptability. 42 U.S.C. § 263a; 42 C.F.R. § 493.1291(c).

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

healthy (or normal). For some analytes that reflect high-prevalence conditions (such as cholesterol), significantly fewer than 95% of the population may be "healthy." In this case, the reference interval may be something other than the central 95% of values.[3]

These specific characteristics represent the primary performance measurements that are used to describe the clinical capabilities of a test. Other measures of clinical validity may be applicable in specific circumstances. For instance, in genetic testing, penetrance may be an element of clinical validity.

Modified LDT

In the draft guidance the FDA proposes that a change in specimen type constitutes an LDT. The CAP recognizes that laboratories may modify for a variety of practical and/or clinical reasons an existing FDA cleared/approved test or an LDT in a minor and non-impactful manner that does not change the intended use of the tests. For example, a laboratory might automate the specimen washing step of an FDA approved test, but the minor modification in method has no impact on the performance or clinical validity of the test. We believe that such non-impactful changes should not constitute the creation of an LDT. We propose the FDA consider several factors on whether a modified FDA approved test kit should qualify for continued enforcement discretion and not be considered an LDT. Those factors are:

- The test uses an existing FDA approved/cleared testing kit;
- The modification does not degrade the analytic performance; and
- The modification does not significantly change the intended use; and
- Additional controls such as proficiency testing are in place.

Furthermore, we believe that laboratories should only be required to demonstrate clinical validity for a change in clinical claims made by the laboratory for any LDT. Laboratories cannot be held responsible for potential "off label" clinical utilization that may evolve downstream. Only if an LDT's intended use is significantly changed by the laboratory, should this be considered a new LDT.

CATEGORIES FOR CONTINUED ENFORCEMENT DISCRETION

The CAP believes that low-risk LDTs as defined by the CAP LDT proposal should continue under the FDA's enforcement discretion policy. The CAP defines LDT low-risk categories as:

- The test result is typically used in conjunction with other clinical findings to establish or confirm diagnosis.
- No claim about a test result alone determines prognosis or direction of therapy.
- The consequence of an incorrect result or incorrect interpretation is unlikely to lead to serious morbidity/mortality.

[3] CLSI. *Clinical Evaluation of Immunoassays*; Approved Guidelines-Second Edition. CLSI Document I/LA21-A2. Wayne, PA: Clinical and Laboratory Standard Institute; 2008.

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

Included in our low-risk classifications are traditional LDTs and LDTs for rare diseases; therefore, the CAP would support inclusion of these categories for continued enforcement discretion from all FDA regulatory requirements. However, we believe the category of traditional LDTs is ill-defined and needs to be more reflective of today's practice. We welcome the opportunity to discuss this point further in order to gain agreement on a definition. For rare diseases, we believe the definition of rare diseases should be based on incidence of the disease instead of volume of testing.

We recommend the FDA use the Rare Disease Act of 2002[4] definition for rare diseases and resources provided by the Office of Rare Diseases Research (ORDR) to help laboratories identify the applicable tests for this category.

The CAP also believes non-impactful modifications to existing low-risk LDTs (as defined by CAP) should be classified as low-risk LDTs and continued under the FDA's enforcement discretion policy.

Process for Classification and Prioritization

The FDA plans to rely on the existing medical device classification system to evaluate the LDT-risk categories. In addition, the agency intends on considering several factors including whether the LDT is:

- Intended for use in high risk disease/conditions or patient populations
- Used for screening or diagnosis, or the nature of the clinical decision
- Used to conjunction with other information to inform the physician including pathologists in making a clinical decision

The existing FDA medical classifications categories will subject many well-established and validated LDTs to higher-level regulatory requirements. These well-established LDTs already represent the standard of care with required proficiency

testing and professional guidelines written for recommended performance and interpretation.

The CAP believes LDTs should be classified based on patient risk, the laboratory's claims for the test, and the potential for harm to patients in instances of an incorrect or misinterpreted test. Our LDT risk classifications are defined as:

- High-risk
    - Test result predicts risk, progression of, or patient eligibility for a specific therapy; AND
    - Test uses proprietary algorithms or computations.

[4] A rare disease or disorder is defined in the U.S. as one affecting fewer than 200,000 Americans. PUBLIC LAW 107–280

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

- Moderate-risk
  - Test result is typically used for diagnosis, predicting disease progression or identifying whether a patient is eligible for a specific therapy.
  - Laboratory may make claims which determine prognosis or direction of therapy.
- Low-risk
  - The test result is typically used in conjunction with other clinical findings to establish or confirm diagnosis.
  - No claim about a test result alone determines prognosis or direction of therapy.
  - The consequence of an incorrect result or incorrect interpretation is unlikely to lead to serious morbidity/mortality.

We are concerned about the FDA's definition of high risk LDTs. The CAP estimates that at least 1,000 LDTs would be classified as equivalent to existing companion diagnostics under the FDA's draft guidance and therefore classified as high-risk LDTs. The CAP is concerned that if the FDA guidance is adopted without modification, it would subject many LDTs – which are well-established in medical practice and represent the standard of care – to the PMA process. The CAP believes that categorizing too many tests as high risk LDTs, including well-established companion diagnostics, will harm patients by limiting access to testing or delaying testing results and increasing healthcare costs.

The CAP urges the FDA to modify its risk classification category to narrow the focus of its regulatory oversight to those truly high-risk LDTs that rely on proprietary algorithms. We welcome the opportunity to discuss the risk classification of companion diagnostics further in order to gain agreement on appropriate classifications of these tests. Furthermore, we believe, in addition to the existing medical device classification system that the FDA should consider several additional criteria such as:

- Risk of the LDTs to patients;
- Clinical claims of the tests;
- Availability of external quality assessment;
- Established as the standard of care or integrated into clinical practice guidelines; and
- Direct involvement of physicians including pathologists in diagnostic interpretations of LDTs.

QUALITY SYSTEMS REGULATIONS

The Quality Systems Regulation (QSR) was developed to define minimal quality system requirements that medical device manufacturers must implement in order to assure that the finished device will be safe and effective. There is a close parallel with the CLIA requirements that are intended to assure the reliability and accuracy of laboratories results; however, significant differences exist between the two regulations.

The CAP performed a crosswalk between CLIA and QSR (see Appendix B) and found

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

significant overlap. As a result, we are concerned that requiring laboratories to comply with the QSR would be duplicative, costly, and burdensome because laboratories would need to implement new processes and procedures as well as hire additional staff in order to comply. We believe the FDA should utilize the CLIA process to avoid the duplication and incorporate the discrete QSR requirements into the CLIA inspection process in order to allow laboratories to adapt existing processes. We also recommend that the QSR requirements should apply only to high-risk LDTs as defined by the CAP and be phased-in at minimum over a two-year survey cycle (ie, laboratories' would need to be in compliance as of the next survey date after the guidance is finalized).

We also believe that moderate-risk LDTs should continue to rely on the CLIA process to assure compliance with the CAP proposed approach. In addition, we believe that the following QSR requirements are not applicable to laboratories because they involve the production and distribution of a "finished device."

- Labeling and packaging control
- Distribution
- Installation
- Device master record
- Device history record
- Servicing

The FDA will need to provide comprehensive information and educational for laboratories to comply with the QSR requirements. For example, when new CLIA requirements are implemented, the CAP conducts online inspector team leader and team member training. The CAP also conducts webinars, such as our *Focus on Compliance* webinar series, to educate laboratories on a periodic basis as to changes in compliance requirements. We believe the FDA will need to offer similar educational opportunities for laboratories to enable understanding and compliance.

CONCLUSION

The CAP believes any LDT oversight framework should be a risk-based model employing a public-private partnership to address oversight of LDTs in a rational, inclusive, and systematic way. In addition, we believe any approach should rely on third-party accreditors and inspectors to oversee and monitor standards for low- and moderate-risk LDTs through the existing CLIA regulatory processes. We believe high-risk LDTs, as defined by CAP, would be reviewed directly by the FDA.

For the agency to achieve its goal, we believe the final guidance should include:

- A broader LDT definition that defines multiple laboratory sites within an integrated healthcare system under common ownership as a single laboratory;
- Enforcement Discretion categories that include rare diseases, traditional LDT's, low-risk LDTs for unmet needs, and modified FDA approved/cleared kits;
- Risk classification mitigation criteria particularly for companion diagnostics; and
- Harmonization between CLIA and QSR requirements.

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

The CAP welcomes the opportunity to work with the FDA to address oversight of LDTs by developing appropriate regulations and policies to allow innovative test development and patient access while assuring public health and safety. Please contact Helena Duncan, CAP Assistant Director, Economic and Regulatory Affairs at hduncan@cap.org if you have any questions on these comments.

Sincerely,

Gene N. Herbek MD, FCAP
President, College of American Pathologists

Enclosure(s): 2
Sent via www.regulations.gov

Helena Duncan
Assistant Director, ERA
t: 800-323-4040 ext. 7100
d: 202-354-7131
f: 202-354-8131
hduncan@cap.org
325 Waukegan Rd.
Northfield, IL 60093
800-323-4040 | cap.org

College of American Pathologists

Office of Government
and Professional Affairs
1350 I Street, NW, Suite 590
Washington, D.C. 20005

Proposed Approach to Oversight of Laboratory Developed Tests

The CAP believes that the following features should be included in any oversight framework for LDTs:

- Tiered, risk-based regulation;
- Assurance of both analytic and clinical validity;
- Evaluation of risk based on the laboratory's claims. Risk defined as the potential for harm to patients of an incorrect or misinterpreted result when the test is ordered consistent with the laboratory's claims;
- CMS oversight of clinical laboratory quality under CLIA;
- Monitoring of laboratories offering low risk LDTs* by CMS-deemed accreditors to ensure laboratory maintains adequate analytical and clinical validation;
- Prior review and approval of moderate risk LDTs* by CMS-deemed accreditors to ensure that the laboratory has adequately validated the test analytically and clinically before testing is used in patient care;
- Targeted FDA review and approval of clinical claims for only high-risk LDTs,* with oversight of compliance by laboratories performing high risk LDTs by CMS and CMS-deemed accreditors;
- Coordination between FDA and CMS to avoid duplicative or unduly burdensome requirements on laboratories;
- Regulatory flexibility to encourage innovation of new diagnostic and predictive tests to promote and protect public health;
- Ability of laboratory personnel to engage in patient-specific communications with physicians regarding test selection and interpretation.

LDTs include the following features:

a. Test is developed within a CLIA-certified laboratory;
b. Test is performed by the clinical laboratory in which the test was developed; and
c. Test is neither FDA-cleared nor FDA-approved, but may incorporate FDA approved/cleared components including modified kits.

** LDTs subject to these requirements are limited to those introduced for clinical testing after April 23, 2003.*

Classification	Determining Factors	Oversight
Low Risk: the consequence of an incorrect result or incorrect interpretation is unlikely to lead to serious morbidity/mortality.	The test result is typically used in conjunction with other clinical findings to establish or confirm diagnosis. No claim that the test result alone determines prognosis or direction of therapy.	The laboratory internally performs analytical validation and determines adequacy of clinical validation prior to offering for clinical testing. The accreditor during the normally scheduled inspections will verify that the laboratory performed appropriate validation studies.
Moderate Risk: the consequence of an incorrect result or incorrect interpretation may lead to serious morbidity/mortality AND the test methodology is well understood and independently verifiable.	The test result is often used for predicting disease progression or identifying whether a patient is eligible for a specific therapy. The laboratory may make claims about clinical accuracy.	The laboratory must submit validation studies to the CMS-deemed accreditor for review and the accreditor must make a determination that there is adequate evidence of analytical and clinical validity before the laboratory may offer the test clinically.
High Risk: the consequence of an incorrect result or incorrect interpretation could lead to serious morbidity/mortality AND the test methodology is not well understood or is not independently verifiable.	The test is used to predict risk of, progression of, or patient eligibility for a specific therapy to treat a disease associated with significant morbidity or mortality, AND; The test methodology uses proprietary algorithms or computations such that the test result cannot be tied to the methods used or inter-laboratory comparisons cannot be performed.	The laboratory must submit test to FDA for review prior to offering the test clinically. CMS and accreditor determine compliance.

COLLEGE of AMERICAN PATHOLOGISTS

Quality Systems-CLIA Crosswalk

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

PART 820 QUALITY SYSTEM REGULATION

FDA REGULATIONS	CLIA	COMMENTS
General provisions		
Scope - 820.1 – See Appendix A		
Definitions - 820.3 – See Appendix B		
Quality Systems - 820.5 Each manufacturer shall establish and maintain a quality system that is appropriate for the specific medical device(s) designed or manufactured, and that meets the requirements of this part.	**493.1249** (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the preanalytic systems specified at §§493.1241 through 493.1242. (b) The preanalytic systems assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of preanalytic systems quality assessment reviews with appropriate staff. (c) The laboratory must document all preanalytic systems quality assessment activities.	

FDA REGULATIONS	CLIA	COMMENTS
	493.1289 (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the analytic systems specified in §§493.1251 through 493.1283. (b) The analytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of analytic systems quality assessment reviews with appropriate staff. (c) The laboratory must document all analytic systems assessment activities. **493.1299** (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess and, when indicated, correct problems identified in the postanalytic systems specified in §493.1291. (b) The postanalytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of postanalytic systems quality assessment reviews with	

FDA REGULATIONS	CLIA	COMMENTS
	appropriate staff. (c) The laboratory must document all postanalytic systems quality assessment activities.	
QS Requirements		
Management responsibility - 820.20 (a) *Quality policy.* Management with executive responsibility shall establish its policy and objectives for, and commitment to, quality. Management with executive responsibility shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization. (b) *Organization.* Each manufacturer shall establish and maintain an adequate organizational structure to ensure that devices are designed and produced in accordance with the requirements of this part. (1) *Responsibility and authority.* Each manufacturer shall establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality, and provide the independence and authority necessary to perform these tasks. (2) *Resources.* Each manufacturer shall provide adequate resources, including the assignment of trained personnel, for management, performance of work, and assessment activities, including	**493.1407** (e) The laboratory director must-- (e)(1) Ensure that testing systems developed and used for each of the tests performed in the laboratory provide quality laboratory services for all aspects of test performance, which includes the preanalytic, analytic, and postanalytic phases of testing; **493.1445** The laboratory director is responsible for the overall operation and administration of the laboratory, including the employment of personnel who are competent to perform test procedures, and record and report test results promptly, accurate, and proficiently and for assuring compliance with the applicable regulations. a) The laboratory director, if qualified, may perform the duties of the technical consultant, clinical consultant, and testing personnel, or delegate these responsibilities to personnel meeting the qualifications of §§493.1409, 493.1415, and 493.1421, respectively.	

FDA REGULATIONS	CLIA	COMMENTS
internal quality audits, to meet the requirements of this part. (3) *Management representative.* Management with executive responsibility shall appoint, and document such appointment of, a member of management who, irrespective of other responsibilities, shall have established authority over and responsibility for: (i) Ensuring that quality system requirements are effectively established and effectively maintained in accordance with this part; and (ii) Reporting on the performance of the quality system to management with executive responsibility for review. (c) *Management review.* Management with executive responsibility shall review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements of this part and the manufacturer's established quality policy and objectives. The dates and results of quality system reviews shall be documented. (d) *Quality planning.* Each manufacturer shall establish a quality plan which defines the quality practices, resources, and activities relevant to devices that	(b) If the laboratory director reapportions performance of his or her responsibilities, he or she remains responsible for ensuring that all duties are properly performed. (e)(11) Employ a sufficient number of laboratory personnel with the appropriate education and either experience or training to provide appropriate consultation, properly supervise and accurately perform tests and report test results in accordance with the personnel responsibilities described in this subpart; **493.1249** (b) The preanalytic systems assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of preanalytic systems quality assessment reviews with appropriate staff. **493.1289** (b) The analytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of analytic systems quality	

FDA REGULATIONS	CLIA	COMMENTS
are designed and manufactured. The manufacturer shall establish how the requirements for quality will be met. (e) *Quality system procedures.* Each manufacturer shall establish quality system procedures and instructions. An outline of the structure of the documentation used in the quality system shall be established where appropriate.	assessment reviews with appropriate staff. **493.1299** (b) The postanalytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of postanalytic systems quality assessment reviews with appropriate staff.	
quality audit - 820.22 Each manufacturer shall establish procedures for quality audits and conduct such audits to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system. Quality audits shall be conducted by individuals who do not have direct responsibility for the matters being audited. Corrective action(s), including a reaudit of deficient matters, shall be taken when necessary. A report of the results of each quality audit, and reaudit(s) where taken, shall be made and such reports shall be reviewed by management having responsibility for the matters audited. The dates and results of quality audits and reaudits shall be documented.	**493.1239** (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and, when indicated, correct problems identified in the general laboratory systems requirements specified at §§493.1231 through 493.1236.	
personnel - 820.25	**493.1407** (e)(10) Employ a sufficient number of	

FDA REGULATIONS	CLIA	COMMENTS
(a) *General.* Each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all activities required by this part are correctly performed. (b) *Training.* Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented. (1) As part of their training, personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs. (2) Personnel who perform verification and validation activities shall be made aware of defects and errors that may be encountered as part of their job functions.	laboratory personnel with the appropriate education and either experience or training to provide appropriate consultation, properly supervise and accurately perform tests and report test results in accordance with the personnel responsibilities described in this subpart; (e)(11) Ensure that prior to testing patients' specimens, all personnel have the appropriate education and experience, receive the appropriate training for the type and complexity of the services offered, and have demonstrated that they can perform all testing operations reliably to provide and report accurate results; **493.1451** (b)(7) Technical Supervisor Responsibilities. Identifying training needs and assuring that each individual performing tests receives regular in-service training and education appropriate for the type and complexity of the laboratory services performed;	
Design Control		
Design control - 820.30 (a) *General.* (1) Each manufacturer of any class III or class II device, and the class I devices listed in paragraph (a)(2) of this section, shall establish and maintain procedures to control the		This section left intentionally blank

FDA REGULATIONS	CLIA	COMMENTS

design of the device in order to ensure that specified design requirements are met.

(2) The following class I devices are subject to design controls:

(i) Devices automated with computer software; and

(ii) The devices listed in the following chart.

Section	Device
868.6810	Catheter, Tracheobronchial Suction.
878.4460	Glove, Surgeon's.
880.6760	Restraint, Protective.
892.5650	System, Applicator, Radionuclide, Manual.
892.5740	Source, Radionuclide Teletherapy.

(b) *Design and development planning.* Each manufacturer shall establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation. The plans shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process. The plans shall be reviewed, updated, and approved as design and

FDA REGULATIONS	CLIA	COMMENTS
development evolves. (c) *Design input.* Each manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. The procedures shall include a mechanism for addressing incomplete, ambiguous, or conflicting requirements. The design input requirements shall be documented and shall be reviewed and approved by a designated individual(s). The approval, including the date and signature of the individual(s) approving the requirements, shall be documented. (d) *Design output.* Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements. Design output procedures shall contain or make reference to acceptance criteria and shall ensure that those design outputs that are essential for the proper functioning of the device are identified. Design output shall be documented, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented. (e) *Design review.* Each manufacturer		

FDA REGULATIONS	CLIA	COMMENTS
shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development. The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed. The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the design history file (the DHF). (f) *Design verification.* Each manufacturer shall establish and maintain procedures for verifying the device design. Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF. (g) *Design validation.* Each manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating		

FDA REGULATIONS	CLIA	COMMENTS
conditions on initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF. (h) *Design transfer.* Each manufacturer shall establish and maintain procedures to ensure that the device design is correctly translated into production specifications. (i) *Design changes.* Each manufacturer shall establish and maintain procedures for the identification, documentation, validation or where appropriate verification, review, and approval of design changes before their implementation. (j) *Design history file.* Each manufacturer shall establish and maintain a DHF for each type of device. The DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the		

FDA REGULATIONS	CLIA	COMMENTS
requirements of this part.		
Document Control		
Document Control - 820.40 Each manufacturer shall establish and maintain procedures to control all documents that are required by this part. The procedures shall provide for the following: (a) *Document approval and distribution.* Each manufacturer shall designate an individual(s) to review for adequacy and approve prior to issuance all documents established to meet the requirements of this part. The approval, including the date and signature of the individual(s) approving the document, shall be documented. Documents established to meet the requirements of this part shall be available at all locations for which they are designated, used, or otherwise necessary, and all obsolete documents shall be promptly removed from all points of use or otherwise prevented from unintended use. (b) *Document changes.* Changes to documents shall be reviewed and approved by an individual(s) in the same function or organization that performed the original review and approval, unless specifically designated otherwise. Approved changes shall be	**493.1251** (a) A written procedures manual for all tests, assays, and examinations performed by the laboratory must be available to, and followed by, laboratory personnel. Textbooks may supplement but not replace the laboratory's written procedures for testing or examining specimens. (d) Procedures and changes in procedures must be approved, signed, and dated by the current laboratory director before use. e) The laboratory must maintain a copy of each procedure with the dates of initial use and discontinuance as described in §493.1105(a)(2).	

FDA REGULATIONS	CLIA	COMMENTS
communicated to the appropriate personnel in a timely manner. Each manufacturer shall maintain records of changes to documents. Change records shall include a description of the change, identification of the affected documents, the signature of the approving individual(s), the approval date, and when the change becomes effective.		
Purchasing Control		
Purchasing Control - 820.50 Each manufacturer shall establish and maintain procedures to ensure that all purchased or otherwise received product and services conform to specified requirements. (a) *Evaluation of suppliers, contractors, and consultants.* Each manufacturer shall establish and maintain the requirements, including quality requirements, that must be met by suppliers, contractors, and consultants. Each manufacturer shall: (1) Evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements. The evaluation shall be documented. (2) Define the type and extent of control to be exercised over the product,	493.1252 a) Test systems must be selected by the laboratory. The testing must be performed following the manufacturer's instructions and in a manner that provides test results within the laboratory's stated performance specifications for each test system as determined under §493.1253.	

FDA REGULATIONS	CLIA	COMMENTS
services, suppliers, contractors, and consultants, based on the evaluation results. (3) Establish and maintain records of acceptable suppliers, contractors, and consultants. (b) *Purchasing data.* Each manufacturer shall establish and maintain data that clearly describe or reference the specified requirements, including quality requirements, for purchased or otherwise received product and services. Purchasing documents shall include, where possible, an agreement that the suppliers, contractors, and consultants agree to notify the manufacturer of changes in the product or service so that manufacturers may determine whether the changes may affect the quality of a finished device. Purchasing data shall be approved in accordance with 820.40.		
Identification and Traceability		
Identification - 820.60 Each manufacturer shall establish and maintain procedures for identifying product during all stages of receipt, production, distribution, and installation to prevent mixups.	**493.1242** (a) The laboratory must establish and follow written policies and procedures for each of the following, if applicable: (a)(3) Specimen labeling, including patient name or unique patient identifier and, when appropriate, specimen source.	
Traceability - 820.65 Each manufacturer of a device that is intended for surgical implant into the	**493.1283** Test Records (a) The laboratory must maintain an	

FDA REGULATIONS	CLIA	COMMENTS
body or to support or sustain life and whose failure to perform when properly used in accordance with instructions for use provided in the labeling can be reasonably expected to result in a significant injury to the user shall establish and maintain procedures for identifying with a control number each unit, lot, or batch of finished devices and where appropriate components. The procedures shall facilitate corrective action. Such identification shall be documented in the DHR.	information or record system that includes the following: (a)(1) The positive identification of the specimen. (a)(2) The date and time of specimen receipt into the laboratory. (a)(3) The condition and disposition of specimens that do not meet the laboratory's criteria for specimen acceptability. (a)(4) The records and dates of all specimen testing, including the identity of the personnel who performed the test(s).	
Production and Process Controls		
Production and process controls - 820.70 (a) *General.* Each manufacturer shall develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications. Where deviations from device specifications could occur as a result of the manufacturing process, the manufacturer shall establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications. Where process controls are needed they shall include: (1) Documented instructions, standard operating procedures (SOP's), and methods that define and control the manner of production;	**493.1256** (a) For each test system, the laboratory is responsible for having control procedures that monitor the accuracy and precision of the complete analytic process. (b) The laboratory must establish the number, type, and frequency of testing control materials using, if applicable, the performance specifications verified or established by the laboratory as specified in §493.1253(b)(3). (c) The control procedures must-- (c)(1) Detect immediate errors that occur due to test system failure, adverse environmental conditions, and operator performance. (c)(2) Monitor over time the accuracy and precision of test performance that may be influenced by changes in test	

FDA REGULATIONS	CLIA	COMMENTS
(2) Monitoring and control of process parameters and component and device characteristics during production; (3) Compliance with specified reference standards or codes; (4) The approval of processes and process equipment; and (5) Criteria for workmanship which shall be expressed in documented standards or by means of identified and approved representative samples. (b) *Production and process changes.* Each manufacturer shall establish and maintain procedures for changes to a specification, method, process, or procedure. Such changes shall be verified or where appropriate validated according to 820.75, before implementation and these activities shall be documented. Changes shall be approved in accordance with 820.40. (c) *Environmental control.* Where environmental conditions could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures to adequately control these environmental conditions. Environmental control system(s) shall be periodically inspected to verify that the system, including necessary equipment, is adequate and functioning properly. These activities shall be documented	system performance and environmental conditions, and variance in operator performance. **493.1239** (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and, when indicated, correct problems identified in the general laboratory systems requirements specified at §§493.1231 through 493.1236. **493.1101** (a) The laboratory must be constructed, arranged, and maintained to ensure the following: (a)(1) The space, ventilation, and utilities necessary for conducting all phases of the testing process. (d) Safety procedures must be established, accessible, and observed to ensure protection from physical, chemical, biochemical, and electrical hazards, and biohazardous materials. **493.1254** (a) Unmodified manufacturer's equipment, instruments, or test systems. The laboratory must perform and document the following: (a)(1) Maintenance as defined by the manufacturer and with at least the frequency specified by the	

FDA REGULATIONS	CLIA	COMMENTS
and reviewed. (d) *Personnel.* Each manufacturer shall establish and maintain requirements for the health, cleanliness, personal practices, and clothing of personnel if contact between such personnel and product or environment could reasonably be expected to have an adverse effect on product quality. The manufacturer shall ensure that maintenance and other personnel who are required to work temporarily under special environmental conditions are appropriately trained or supervised by a trained individual. (e) *Contamination control.* Each manufacturer shall establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality. (f) *Buildings.* Buildings shall be of suitable design and contain sufficient space to perform necessary operations, prevent mixups, and assure orderly handling. (g) *Equipment.* Each manufacturer shall ensure that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use.	manufacturer. (a)(2) Function checks as defined by the manufacturer and with at least the frequency specified by the manufacturer. Function checks must be within the manufacturer's established limits before patient testing is conducted. (b) *Equipment, instruments, or test systems developed in-house, commercially available and modified by the laboratory, or maintenance and function check protocols are not provided by the manufacturer.* The laboratory must do the following: (b)(1)(i) Establish a maintenance protocol that ensures equipment, instrument, and test system performance that is necessary for accurate and reliable test results and test result reporting. (b)(1)(ii) Perform and document the maintenance activities specified in paragraph (b)(1)(i) of this section. (b)(2)(i) Define a function check protocol that ensures equipment, instrument, and test system performance that is necessary for accurate and reliable test results and test result reporting. (b)(2)(ii) Perform and document the function checks, including background or baseline checks, specified in paragraph (b)(2)(i) of this section. Function checks must be within the	

FDA REGULATIONS	CLIA	COMMENTS
(1) *Maintenance schedule.* Each manufacturer shall establish and maintain schedules for the adjustment, cleaning, and other maintenance of equipment to ensure that manufacturing specifications are met. Maintenance activities, including the date and individual(s) performing the maintenance activities, shall be documented. (2) *Inspection.* Each manufacturer shall conduct periodic inspections in accordance with established procedures to ensure adherence to applicable equipment maintenance schedules. The inspections, including the date and individual(s) conducting the inspections, shall be documented. (3) *Adjustment.* Each manufacturer shall ensure that any inherent limitations or allowable tolerances are visibly posted on or near equipment requiring periodic adjustments or are readily available to personnel performing these adjustments. (h) *Manufacturing material.* Where a manufacturing material could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures for the use and removal of such manufacturing material to ensure that it is removed or limited to an amount that does not adversely	laboratory's established limits before patient testing is conducted.	

FDA REGULATIONS	CLIA	COMMENTS
affect the device's quality. The removal or reduction of such manufacturing material shall be documented. (i) *Automated processes.* When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented.		
Inspection, measuring, and test equipment - 820.72 (a) *Control of inspection, measuring, and test equipment.* Each manufacturer shall ensure that all inspection, measuring, and test equipment, including mechanical, automated, or electronic inspection and test equipment, is suitable for its intended purposes and is capable of producing valid results. Each manufacturer shall establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, and maintained. The procedures shall include provisions for handling, preservation, and storage of equipment, so that its accuracy and fitness for use are maintained. These activities shall be documented.	**493.1255** Calibration and calibration verification procedures are required to substantiate the continued accuracy of the test system throughout the laboratory's reportable range of test results for the test system. Unless otherwise specified in this subpart, for each applicable test system the laboratory must do the following: (a) Perform and document calibration procedures-- (a)(1) Following the manufacturer's test system instructions, using calibration materials provided or specified, and with at least the frequency recommended by the manufacturer; (a)(2) Using the criteria verified or established by the laboratory as specified in §493.1253(b)(3)--	

FDA REGULATIONS	CLIA	COMMENTS
(b) *Calibration.* Calibration procedures shall include specific directions and limits for accuracy and precision. When accuracy and precision limits are not met, there shall be provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on the device's quality. These activities shall be documented. (1) *Calibration standards.* Calibration standards used for inspection, measuring, and test equipment shall be traceable to national or international standards. If national or international standards are not practical or available, the manufacturer shall use an independent reproducible standard. If no applicable standard exists, the manufacturer shall establish and maintain an in-house standard. (2) *Calibration records.* The equipment identification, calibration dates, the individual performing each calibration, and the next calibration date shall be documented. These records shall be displayed on or near each piece of equipment or shall be readily available to the personnel using such equipment and to the individuals responsible for calibrating the equipment.	(a)(2)(i) Using calibration materials appropriate for the test system and, if possible, traceable to a reference method or reference material of known value; and (a)(2)(ii) Including the number, type, and concentration of calibration materials, as well as acceptable limits for and the frequency of calibration; and (a)(3) Whenever calibration verification fails to meet the laboratory's acceptable limits for calibration verification. (b) Perform and document calibration verification procedures— (b)(1) Following the manufacturer's calibration verification instructions; (b)(2) Using the criteria verified or established by the laboratory under §493.1253(b)(3)— (b)(2)(i) Including the number, type, and concentration of the materials, as well as acceptable limits for calibration verification; and (b)(2)(ii) Including at least a minimal (or zero) value, a mid-point value, and a maximum value near the upper limit of the range to verify the laboratory's reportable range of test results for the test system; and (b)(3) At least once every 6 months and whenever any of the following occur: (b)(3)(i) A complete change of reagents for a procedure is introduced,	

FDA REGULATIONS	CLIA	COMMENTS
	unless the laboratory can demonstrate that changing reagent lot numbers does not affect the range used to report patient test results, and control values are not adversely affected by reagent lot number changes. (b)(3)(ii) There is major preventive maintenance or replacement of critical parts that may influence test performance. (b)(3)(iii) Control materials reflect an unusual trend or shift, or are outside of the laboratory's acceptable limits, and other means of assessing and correcting unacceptable control values fail to identify and correct the problem. (b)(3)(iv) The laboratory's established schedule for verifying the reportable range for patient test results requires more frequent calibration verification. **493.1254** (a) Unmodified manufacturer's equipment, instruments, or test systems. The laboratory must perform and document the following: (a)(1) Maintenance as defined by the manufacturer and with at least the frequency specified by the manufacturer. (a)(2) Function checks as defined by the manufacturer and with at least the frequency specified by the manufacturer. Function checks must be	

FDA REGULATIONS	CLIA	COMMENTS
	within the manufacturer's established limits before patient testing is conducted. (b) *Equipment, instruments, or test systems developed in-house, commercially available and modified by the laboratory, or maintenance and function check protocols are not provided by the manufacturer.* The laboratory must do the following: (b)(1)(i) Establish a maintenance protocol that ensures equipment, instrument, and test system performance that is necessary for accurate and reliable test results and test result reporting. (b)(1)(ii) Perform and document the maintenance activities specified in paragraph (b)(1)(i) of this section. (b)(2)(i) Define a function check protocol that ensures equipment, instrument, and test system performance that is necessary for accurate and reliable test results and test result reporting. (b)(2)(ii) Perform and document the function checks, including background or baseline checks, specified in paragraph (b)(2)(i) of this section. Function checks must be within the laboratory's established limits before patient testing is conducted.	
Process validation - 820.75 (a) Where the results of a process cannot	**493.1253** (b)(1) *Verification of performance specifications.* Each laboratory that	

FDA REGULATIONS	CLIA	COMMENTS
be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented. (b) Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met. (1) Each manufacturer shall ensure that validated processes are performed by qualified individual(s). (2) For validated processes, the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used shall be documented. (c) When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented.	introduces an unmodified, FDA-cleared or approved test system must do the following before reporting patient test results: (b)(1)(i) Demonstrate that it can obtain performance specifications comparable to those established by the manufacturer for the following performance characteristics: (b)(1)(i)(A) Accuracy. (b)(1)(i)(B) Precision. (b)(1)(i)(C) Reportable range of test results for the test system. (b)(1)(ii) Verify that the manufacturer's reference intervals (normal values) are appropriate for the laboratory's patient population. (b)(2) *Establishment of performance specifications.* Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as text book procedures, or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable: (b)(2)(i) Accuracy. (b)(2)(ii) Precision.	

FDA REGULATIONS	CLIA	COMMENTS
	(b)(2)(iii) Analytical sensitivity. (b)(2)(iv) Analytical specificity to include interfering substances. (b)(2)(v) Reportable range of test results for the test system. (b)(2)(vi) Reference intervals (normal values). (b)(2)(vii) Any other performance characteristic required for test performance. (b)(3) *Determination of calibration and control procedures.* The laboratory must determine the test system's calibration procedures and control procedures based upon the performance specifications verified or established under paragraph (b)(1) or (b)(2) of this section. *(c) Documentation.* The laboratory must document all activities specified in this section.	
Acceptance Activities		
Receiving, in-process, and finished device acceptance - 820.80 (a) *General.* Each manufacturer shall establish and maintain procedures for acceptance activities. Acceptance activities include inspections, tests, or other verification activities. (b) *Receiving acceptance activities.* Each manufacturer shall establish and maintain procedures for acceptance of incoming product. Incoming product shall be inspected,	**493.1256** (f) Control Procedures Results of control materials must meet the laboratory's and, as applicable, the manufacturer's test system criteria for acceptability before reporting patient test results. (d)(6) Control Procedures Perform control material testing as specified in this paragraph before resuming patient testing when a complete change of reagents is	

FDA REGULATIONS	CLIA	COMMENTS
tested, or otherwise verified as conforming to specified requirements. Acceptance or rejection shall be documented. (c) *In-process acceptance activities.* Each manufacturer shall establish and maintain acceptance procedures, where appropriate, to ensure that specified requirements for in-process product are met. Such procedures shall ensure that in-process product is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received, and are documented. (d) *Final acceptance activities.* Each manufacturer shall establish and maintain procedures for finished device acceptance to ensure that each production run, lot, or batch of finished devices meets acceptance criteria. Finished devices shall be held in quarantine or otherwise adequately controlled until released. Finished devices shall not be released for distribution until: (1) The activities required in the DMR are completed; (2) the associated data and documentation is reviewed; (3) the release is authorized by the signature of a designated individual(s);	introduced; major preventive maintenance is performed; or any critical part that may influence test performance is replaced. (d)(1)Control Procedures Perform control procedures as defined in this section unless otherwise specified in the additional specialty and subspecialty requirements at §§493.1261 through 493.1278. (d)(2) Control Procedures For each test system, perform control procedures using the number and frequency specified by the manufacturer or established by the laboratory when they meet or exceed the requirements in paragraph (d)(3) of this section. (d)(3) Control Procedures At least once each day patient specimens are assayed or examined perform the following for— (d)(3)(i) Each quantitative procedure, include two control materials of different concentrations; (d)(3)(ii) Each qualitative procedure, include a negative and positive control material;	

FDA REGULATIONS	CLIA	COMMENTS
and (4) the authorization is dated. (e) *Acceptance records.* Each manufacturer shall document acceptance activities required by this part. These records shall include: (1) The acceptance activities performed; (2) the dates acceptance activities are performed; (3) the results; (4) the signature of the individual(s) conducting the acceptance activities; and (5) where appropriate the equipment used. These records shall be part of the DHR.		
Acceptance Status - 820.86 Each manufacturer shall identify by suitable means the acceptance status of product, to indicate the conformance or nonconformance of product with acceptance criteria. The identification of acceptance status shall be maintained throughout manufacturing, packaging, labeling, installation, and servicing of the product to ensure that only product which has passed the required acceptance activities is distributed, used, or installed.		This section left intentionally blank
Nonconforming Products		

FDA REGULATIONS	CLIA	COMMENTS
Nonconforming Products - 820.90 (a) *Control of nonconforming product.* Each manufacturer shall establish and maintain procedures to control product that does not conform to specified requirements. The procedures shall address the identification, documentation, evaluation, segregation, and disposition of nonconforming product. The evaluation of nonconformance shall include a determination of the need for an investigation and notification of the persons or organizations responsible for the nonconformance. The evaluation and any investigation shall be documented. (b) *Nonconformity review and disposition.* (1) Each manufacturer shall establish and maintain procedures that define the responsibility for review and the authority for the disposition of nonconforming product. The procedures shall set forth the review and disposition process. Disposition of nonconforming product shall be documented. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use. (2) Each manufacturer shall establish and maintain procedures for rework, to include retesting and reevaluation of the		This section left intentionally blank

FDA REGULATIONS	CLIA	COMMENTS
nonconforming product after rework, to ensure that the product meets its current approved specifications. Rework and reevaluation activities, including a determination of any adverse effect from the rework upon the product, shall be documented in the DHR.		
Corrective and Preventive Actions		
Corrective and Preventive Actions - 820.100 (a) Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for: (1) Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems; (2) Investigating the cause of nonconformities relating to product, processes, and the quality system; (3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;	**493.1249** (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the preanalytic systems specified at §§493.1241 through 493.1242. (b) The preanalytic systems assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of preanalytic systems quality assessment reviews with appropriate staff. (c) The laboratory must document all preanalytic systems quality assessment activities. **493.1289** (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct	

FDA REGULATIONS	CLIA	COMMENTS
(4) Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device; (5) Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems; (6) Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems; and (7) Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review. (b) All activities required under this section, and their results, shall be documented.	problems identified in the analytic systems specified in §§493.1251 through 493.1283. (b) The analytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of analytic systems quality assessment reviews with appropriate staff. (c) The laboratory must document all analytic systems assessment activities. **493.1299** (a) The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess and, when indicated, correct problems identified in the postanalytic systems specified in §493.1291. (b) The postanalytic systems quality assessment must include a review of the effectiveness of corrective actions taken to resolve problems, revision of policies and procedures necessary to prevent recurrence of problems, and discussion of postanalytic systems quality assessment reviews with appropriate staff. (c) The laboratory must document all postanalytic systems quality assessment activities.	

FDA REGULATIONS	CLIA	COMMENTS
Labeling and Packaging Control		
Device labeling - 820.120 Each manufacturer shall establish and maintain procedures to control labeling activities. (a) *Label integrity.* Labels shall be printed and applied so as to remain legible and affixed during the customary conditions of processing, storage, handling, distribution, and where appropriate use. (b) *Labeling inspection.* Labeling shall not be released for storage or use until a designated individual(s) has examined the labeling for accuracy including, where applicable, the correct unique device identifier (UDI) or universal product code (UPC), expiration date, control number, storage instructions, handling instructions, and any additional processing instructions. The release, including the date and signature of the individual(s) performing the examination, shall be documented in the DHR. (c) *Labeling storage.* Each manufacturer shall store labeling in a manner that provides proper identification and is designed to prevent mixups. (d) *Labeling operations.* Each manufacturer shall control labeling and packaging operations to prevent labeling mixups. The label and labeling used for each production unit, lot, or		This section left intentionally blank

FDA REGULATIONS	CLIA	COMMENTS
batch shall be documented in the DHR. (e) *Control number.* Where a control number is required by 820.65, that control number shall be on or shall accompany the device through distribution.		
Device packaging - 820.130 Each manufacturer shall ensure that device packaging and shipping containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution.		This section left intentionally blank
Handling, storage, distribution, and installation		
Handling - 820.140 Each manufacturer shall establish and maintain procedures to ensure that mixups, damage, deterioration, contamination, or other adverse effects to product do not occur during handling.	**493.1101** (a) The laboratory must be constructed, arranged, and maintained to ensure the following: (a)(1) The space, ventilation, and utilities necessary for conducting all phases of the testing process. (a)(2) Contamination of patient specimens, equipment, instruments, reagents, materials, and supplies is minimized.	
Storage - 820.150 (a) Each manufacturer shall establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mixups, damage, deterioration, contamination, or other adverse effects pending use or	**493.1101** (a) The laboratory must be constructed, arranged, and maintained to ensure the following: (a)(1) The space, ventilation, and utilities necessary for conducting all phases of the testing process. (a)(2) Contamination of patient	

FDA REGULATIONS	CLIA	COMMENTS
distribution and to ensure that no obsolete, rejected, or deteriorated product is used or distributed. When the quality of product deteriorates over time, it shall be stored in a manner to facilitate proper stock rotation, and its condition shall be assessed as appropriate. (b) Each manufacturer shall establish and maintain procedures that describe the methods for authorizing receipt from and dispatch to storage areas and stock rooms.	specimens, equipment, instruments, reagents, materials, and supplies is minimized.	
Distribution - 820.160 (a) Each manufacturer shall establish and maintain procedures for control and distribution of finished devices to ensure that only those devices approved for release are distributed and that purchase orders are reviewed to ensure that ambiguities and errors are resolved before devices are released for distribution. Where a device's fitness for use or quality deteriorates over time, the procedures shall ensure that expired devices or devices deteriorated beyond acceptable fitness for use are not distributed. (b) Each manufacturer shall maintain distribution records which include or refer to the location of: (1) The name and address of the initial consignee;		This section left intentionally blank

FDA REGULATIONS	CLIA	COMMENTS
(2) The identification and quantity of devices shipped; (3) The date shipped; and (4) Any control number(s) used.		
Installation - 820.170 (a) Each manufacturer of a device requiring installation shall establish and maintain adequate installation and inspection instructions, and where appropriate test procedures. Instructions and procedures shall include directions for ensuring proper installation so that the device will perform as intended after installation. The manufacturer shall distribute the instructions and procedures with the device or otherwise make them available to the person(s) installing the device. (b) The person installing the device shall ensure that the installation, inspection, and any required testing are performed in accordance with the manufacturer's instructions and procedures and shall document the inspection and any test results to demonstrate proper installation.		This section left intentionally blank
Records		
General requirements - 820.180 All records required by this part shall be maintained at the manufacturing establishment or other location that is reasonably accessible to responsible officials of the manufacturer and to	**493.1105** (a) The laboratory must retain its records and, as applicable, slides, blocks, and tissues as follows: (a)(1) Test requisitions and authorizations. Retain records of test	

FDA REGULATIONS	CLIA	COMMENTS
employees of FDA designated to perform inspections. Such records, including those not stored at the inspected establishment, shall be made readily available for review and copying by FDA employee(s). Such records shall be legible and shall be stored to minimize deterioration and to prevent loss. Those records stored in automated data processing systems shall be backed up. (a) *Confidentiality.* Records deemed confidential by the manufacturer may be marked to aid FDA in determining whether information may be disclosed under the public information regulation in part 20 of this chapter. (b) *Record retention period.* All records required by this part shall be retained for a period of time equivalent to the design and expected life of the device, but in no case less than 2 years from the date of release for commercial distribution by the manufacturer. (c) *Exceptions.* This section does not apply to the reports required by 820.20(c) Management review, 820.22 Quality audits, and supplier audit reports used to meet the requirements of 820.50(a) Evaluation of suppliers, contractors, and consultants, but does apply to procedures established under these provisions. Upon request of a	requisitions and test authorizations, including the patient's chart or medical record if used as the test requisition or authorization, for at least 2 years. (a)(2) Test procedures. Retain a copy of each test procedure for at least 2 years after a procedure has been discontinued. Each test procedure must include the dates of initial use and discontinuance. (a)(3) Analytic systems records. Retain quality control and patient test records (including instrument printouts, if applicable) and activities specified in §§493.1252 through 493.1289 for at least 2 years. In addition, retain the following: (a)(3)(i) Records of test system performance specifications that the laboratory establishes or verifies under §493.1253 for the period of time the laboratory uses the test system but no less than 2 years. (a)(3)(ii) Immunohematology records, blood and blood product records, and transfusion records as specified in 21 CFR 606.160(b)(3)(ii), (b)(3)(iv), (b)(3)(v), and (d). (a)(4) Proficiency testing records. Retain all proficiency testing records for at least 2 years. (a)(5) Laboratory quality system assessment records. Retain all laboratory quality system assessment records for at least 2 years. (a)(6) Test reports. Retain or be able to	

FDA REGULATIONS	CLIA	COMMENTS
designated employee of FDA, an employee in management with executive responsibility shall certify in writing that the management reviews and quality audits required under this part, and supplier audits where applicable, have been performed and documented, the dates on which they were performed, and that any required corrective action has been undertaken.	retrieve a copy of the original report (including final, preliminary, and corrected reports) at least 2 years after the date of reporting. In addition, retain the following: (a)(6)(i) Immunohematology reports as specified in 21 CFR 606.160(d). (a)(6)(ii) Pathology test reports for at least 10 years after the date of reporting. (a)(7) Slide, block, and tissue retention-- (a)(7)(i) Slides. (a)(7)(i)(A) Retain cytology slide preparations for at least 5 years from the date of examination (see §493.1274(f) for proficiency testing exception). (a)(7)(i)(B) Retain histopathology slides for at least 10 years from the date of examination. (a)(7)(ii) Blocks. Retain pathology specimen blocks for at least 2 years from the date of examination. (a)(7)(iii) Tissue. Preserve remnants of tissue for pathology examination until a diagnosis is made on the specimen.	
Device master record - 820.181 Each manufacturer shall maintain device master records (DMR's). Each manufacturer shall ensure that each DMR is prepared and approved in accordance with 820.40. The DMR for each type of device shall include, or refer to the location of, the following		This section left intentionally blank

FDA REGULATIONS	CLIA	COMMENTS
information: (a) Device specifications including appropriate drawings, composition, formulation, component specifications, and software specifications; (b) Production process specifications including the appropriate equipment specifications, production methods, production procedures, and production environment specifications; (c) Quality assurance procedures and specifications including acceptance criteria and the quality assurance equipment to be used; (d) Packaging and labeling specifications, including methods and processes used; and (e) Installation, maintenance, and servicing procedures and methods.		
Device history record - 820.184 Each manufacturer shall maintain device history records (DHR's). Each manufacturer shall establish and maintain procedures to ensure that DHR's for each batch, lot, or unit are maintained to demonstrate that the device is manufactured in accordance with the DMR and the requirements of this part. The DHR shall include, or refer to the location of, the following information: (a) The dates of manufacture;		This section left intentionally blank

FDA REGULATIONS	CLIA	COMMENTS
(b) The quantity manufactured; (c) The quantity released for distribution; (d) The acceptance records which demonstrate the device is manufactured in accordance with the DMR; (e) The primary identification label and labeling used for each production unit; and (f) Any unique device identifier (UDI) or universal product code (UPC), and any other device identification(s) and control number(s) used.		
Quality systems record - 820.186 Each manufacturer shall maintain a quality system record (QSR). The QSR shall include, or refer to the location of, procedures and the documentation of activities required by this part that are not specific to a particular type of device(s), including, but not limited to, the records required by 820.20. Each manufacturer shall ensure that the QSR is prepared and approved in accordance with 820.40.		This section left intentionally blank
Complaints files - 820.198 (a) Each manufacturer shall maintain complaint files. Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that:	**493.1233** The laboratory must have a system in place to ensure that it documents all complaints and problems reported to the laboratory. The laboratory must conduct investigations of complaints, when appropriate.	

FDA REGULATIONS	CLIA	COMMENTS
(1) All complaints are processed in a uniform and timely manner; (2) Oral complaints are documented upon receipt; and (3) Complaints are evaluated to determine whether the complaint represents an event which is required to be reported to FDA under part 803 of this chapter, Medical Device Reporting. (b) Each manufacturer shall review and evaluate all complaints to determine whether an investigation is necessary. When no investigation is made, the manufacturer shall maintain a record that includes the reason no investigation was made and the name of the individual responsible for the decision not to investigate. (c) Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated, unless such investigation has already been performed for a similar complaint and another investigation is not necessary. (d) Any complaint that represents an event which must be reported to FDA under part 803 of this chapter shall be promptly reviewed, evaluated, and investigated by a designated individual(s) and shall be maintained in a separate portion of the complaint files or		

FDA REGULATIONS	CLIA	COMMENTS
otherwise clearly identified. In addition to the information required by 820.198(e), records of investigation under this paragraph shall include a determination of: (1) Whether the device failed to meet specifications; (2) Whether the device was being used for treatment or diagnosis; and (3) The relationship, if any, of the device to the reported incident or adverse event. (e) When an investigation is made under this section, a record of the investigation shall be maintained by the formally designated unit identified in paragraph (a) of this section. The record of investigation shall include: (1) The name of the device; (2) The date the complaint was received; (3) Any unique device identifier (UDI) or universal product code (UPC), and any other device identification(s) and control number(s) used; (4) The name, address, and phone number of the complainant; (5) The nature and details of the complaint; (6) The dates and results of the		

FDA REGULATIONS	CLIA	COMMENTS
investigation; (7) Any corrective action taken; and (8) Any reply to the complainant. (f) When the manufacturer's formally designated complaint unit is located at a site separate from the manufacturing establishment, the investigated complaint(s) and the record(s) of investigation shall be reasonably accessible to the manufacturing establishment. (g) If a manufacturer's formally designated complaint unit is located outside of the United States, records required by this section shall be reasonably accessible in the United States at either: (1) A location in the United States where the manufacturer's records are regularly kept; or (2) The location of the initial distributor.		
Servicing		
Servicing - 820.200 (a) Where servicing is a specified requirement, each manufacturer shall establish and maintain instructions and procedures for performing and verifying that the servicing meets the specified requirements. (b) Each manufacturer shall analyze service reports with appropriate		This section left intentionally blank

FDA REGULATIONS	CLIA	COMMENTS
statistical methodology in accordance with 820.100. (c) Each manufacturer who receives a service report that represents an event which must be reported to FDA under part 803 of this chapter shall automatically consider the report a complaint and shall process it in accordance with the requirements of 820.198. (d) Service reports shall be documented and shall include: (1) The name of the device serviced; (2) Any unique device identifier (UDI) or universal product code (UPC), and any other device identification(s) and control number(s) used; (3) The date of service; (4) The individual(s) servicing the device; (5) The service performed; and (6) The test and inspection data.		
Statistical Techniques		
Statistical Techniques - 820.250 (a) Where appropriate, each manufacturer shall establish and maintain procedures for identifying valid statistical techniques required for establishing, controlling, and verifying the acceptability of process capability and product characteristics.	**493.1256** (d)(10) Establish or verify the criteria for acceptability of all control materials. (d)(10)(i) When control materials providing quantitative results are used, statistical parameters (for example, mean and standard deviation) for each batch and lot number of control materials must be defined and	

FDA REGULATIONS	CLIA	COMMENTS
(b) Sampling plans, when used, shall be written and based on a valid statistical rationale. Each manufacturer shall establish and maintain procedures to ensure that sampling methods are adequate for their intended use and to ensure that when changes occur the sampling plans are reviewed. These activities shall be documented.	available. (d)(10)(ii) The laboratory may use the stated value of a commercially assayed control material provided the stated value is for the methodology and instrumentation employed by the laboratory and is verified by the laboratory. (d)(10)(iii) Statistical parameters for unassayed control materials must be established over time by the laboratory through concurrent testing of control materials having previously determined statistical parameters.	

APPENDIX A - SCOPE (21CFR820.1)

(a) *Applicability.* (1) Current good manufacturing practice (CGMP) requirements are set forth in this quality system regulation. The requirements in this part govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, and servicing of all finished devices intended for human use. The requirements in this part are intended to ensure that finished devices will be safe and effective and otherwise in compliance with the Federal Food, Drug, and Cosmetic Act (the act). This part establishes basic requirements applicable to manufacturers of finished medical devices. If a manufacturer engages in only some operations subject to the requirements in this part, and not in others, that manufacturer need only comply with those requirements applicable to the operations in which it is engaged. With respect to class I devices, design controls apply only to those devices listed in 820.30(a)(2). This regulation does not apply to manufacturers of components or parts of finished devices, but such manufacturers are encouraged to use appropriate provisions of this regulation as guidance. Manufacturers of human blood and blood components are not subject to this part, but are subject to part 606 of this chapter. Manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in 1271.3(d) of this chapter, that are medical devices (subject to premarket review or notification, or exempt from notification, under an application submitted under the device provisions of the act or under a biological product license application under section 351 of the Public Health Service Act) are subject to this part and are also subject to the donor-eligibility procedures set forth in part 1271 subpart C of this chapter and applicable current good tissue practice procedures in part 1271 subpart D of this chapter. In the event of a conflict between applicable regulations in part 1271 and in other parts of this chapter, the regulation specifically applicable to the device in question shall supersede the more general.

(2) The provisions of this part shall be applicable to any finished device as defined in this part, intended for human use, that is manufactured, imported, or offered for import in any State or Territory of the United States, the District of Columbia, or the Commonwealth of Puerto Rico.

(3) In this regulation the term "where appropriate" is used several times. When a requirement is qualified by "where appropriate," it is deemed to be "appropriate" unless the manufacturer can document justification otherwise. A requirement is "appropriate" if nonimplementation could reasonably be expected to result in the product not meeting its specified requirements or the manufacturer not being able to carry out any necessary corrective action.

(b) The quality system regulation in this part supplements regulations in other parts of this chapter except where explicitly stated otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the

regulations specifically applicable to the device in question shall supersede any other generally applicable requirements.

(c) *Authority.* Part 820 is established and issued under authority of sections 501, 502, 510, 513, 514, 515, 518, 519, 520, 522, 701, 704, 801, 803 of the act (21 U.S.C. 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 360l, 371, 374, 381, 383). The failure to comply with any applicable provision in this part renders a device adulterated under section 501(h) of the act. Such a device, as well as any person responsible for the failure to comply, is subject to regulatory action.

(d) *Foreign manufacturers.* If a manufacturer who offers devices for import into the United States refuses to permit or allow the completion of a Food and Drug Administration (FDA) inspection of the foreign facility for the purpose of determining compliance with this part, it shall appear for purposes of section 801(a) of the act, that the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation, or servicing of any devices produced at such facility that are offered for import into the United States do not conform to the requirements of section 520(f) of the act and this part and that the devices manufactured at that facility are adulterated under section 501(h) of the act.

(e) *Exemptions or variances.* (1) Any person who wishes to petition for an exemption or variance from any device quality system requirement is subject to the requirements of section 520(f)(2) of the act. Petitions for an exemption or variance shall be submitted according to the procedures set forth in 10.30 of this chapter, the FDA's administrative procedures. Guidance is available from the Food and Drug Administration, Center for Devices and Radiological Health, Division of Small Manufacturers, International and Consumer Assistance, 10903 New Hampshire Ave., Bldg. 66, rm. 4613, Silver Spring, MD 20993-0002, 1-800-638-2041 or 301-796-7100, FAX: 301-847-8149.

(2) FDA may initiate and grant a variance from any device quality system requirement when the agency determines that such variance is in the best interest of the public health. Such variance will remain in effect only so long as there remains a public health need for the device and the device would not likely be made sufficiently available without the variance.

[61 FR 52654, Oct. 7, 1996, as amended at 65 FR 17136, Mar. 31, 2000; 65 FR 66636, Nov. 7, 2000; 69 FR 29829, May 25, 2005; 72 FR 17399, Apr. 9, 2007; 75 FR 20915, Apr. 22, 2010]

APPENDIX B – DEFINITIONS (21CFR820.3)

(a) *Act* means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201-903, 52 Stat. 1040 *et seq.,* as amended (21 U.S.C. 321-394)). All definitions in section 201 of the act shall apply to the regulations in this part.

(b) *Complaint* means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

(c) *Component* means any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device.

(d) *Control number* means any distinctive symbols, such as a distinctive combination of letters or numbers, or both, from which the history of the manufacturing, packaging, labeling, and distribution of a unit, lot, or batch of finished devices can be determined.

(e) *Design history file* (*DHF*) means a compilation of records which describes the design history of a finished device.

(f) *Design input* means the physical and performance requirements of a device that are used as a basis for device design.

(g) *Design output* means the results of a design effort at each design phase and at the end of the total design effort. The finished design output is the basis for the device master record. The total finished design output consists of the device, its packaging and labeling, and the device master record.

(h) *Design review* means a documented, comprehensive, systematic examination of a design to evaluate the adequacy of the design requirements, to evaluate the capability of the design to meet these requirements, and to identify problems.

(i) *Device history record* (*DHR*) means a compilation of records containing the production history of a finished device.

(j) *Device master record* (*DMR*) means a compilation of records containing the procedures and specifications for a finished device.

(k) *Establish* means define, document (in writing or electronically), and implement.

(l) *Finished device* means any device or accessory to any device that is suitable for use or capable of functioning, whether or not it is packaged, labeled, or sterilized.

(m) *Lot or batch* means one or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to

have uniform characteristics and quality within specified limits.

(n) *Management with executive responsibility* means those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer's quality policy and quality system.

(o) *Manufacturer* means any person who designs, manufactures, fabricates, assembles, or processes a finished device. Manufacturer includes but is not limited to those who perform the functions of contract sterilization, installation, relabeling, remanufacturing, repacking, or specification development, and initial distributors of foreign entities performing these functions.

(p) *Manufacturing material* means any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer.

(q) *Nonconformity* means the nonfulfillment of a specified requirement.

(r) *Product* means components, manufacturing materials, in- process devices, finished devices, and returned devices.

(s) *Quality* means the totality of features and characteristics that bear on the ability of a device to satisfy fitness-for-use, including safety and performance.

(t) *Quality audit* means a systematic, independent examination of a manufacturer's quality system that is performed at defined intervals and at sufficient frequency to determine whether both quality system activities and the results of such activities comply with quality system procedures, that these procedures are implemented effectively, and that these procedures are suitable to achieve quality system objectives.

(u) *Quality policy* means the overall intentions and direction of an organization with respect to quality, as established by management with executive responsibility.

(v) *Quality system* means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

(w) *Remanufacturer* means any person who processes, conditions, renovates, repackages, restores, or does any other act to a finished device that significantly changes the finished device's performance or safety specifications, or intended use.

(x) *Rework* means action taken on a nonconforming product so that it will fulfill the specified DMR requirements before it is released for distribution.

(y) *Specification* means any requirement with which a product, process, service, or other activity must conform.

(z) *Validation* means confirmation by examination and provision of objective evidence that the particular requirements for a

specific intended use can be consistently fulfilled.

(1) *Process validation* means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

(2) *Design validation* means establishing by objective evidence that device specifications conform with user needs and intended use(s).

(aa) *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

(bb) *Human cell, tissue, or cellular or tissue-based product (HCT/P) regulated as a device* means an HCT/P as defined in 1271.3(d) of this chapter that does not meet the criteria in 1271.10(a) and that is also regulated as a device.

(cc) *Unique device identifier (UDI)* means an identifier that adequately identifies a device through its distribution and use by meeting the requirements of 830.20 of this chapter. A unique device identifier is composed of:

(1) A *device identifier* --a mandatory, fixed portion of a UDI that identifies the specific version or model of a device and the labeler of that device; and

(2) A *production identifier* --a conditional, variable portion of a UDI that identifies one or more of the following when included on the label of the device:

(i) The lot or batch within which a device was manufactured;

(ii) The serial number of a specific device;

(iii) The expiration date of a specific device;

(iv) The date a specific device was manufactured.

(v) For an HCT/P regulated as a device, the distinct identification code required by 1271.290(c) of this chapter.

(dd) *Universal product code (UPC)* means the product identifier used to identify an item sold at retail in the United States.

[61 FR 52654, Oct. 7, 1996, as amended at 78 FR 55822, Sept. 24, 2013]