86 FDA Regulation of Laboratory-Developed Tests

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AMERICAN SOCIETY FOR CLINICAL PATHOLOGY
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86 FDA Regulation of Laboratory-Developed Tests

Recent efforts by the FDA to regulate laboratory-developed tests (LDT) will be reviewed in this session. A discussion will also feature the potential impact of such regulations on the laboratory community and general public health. The session will also include an over-view of the regulatory process, and things you can start doing now to prepare your laboratory to obtain FDA clearance or approval for your own laboratory-developed tests.

- Discuss the need for FDA regulation of laboratory-developed tests and its potential pitfalls.
- Provide an over-view of the regulatory process.
- Explain how you can prepare to obtain FDA clearance or approval for your laboratory-developed test by introducing Design Controls in your laboratory, and by submitting a pre-IDE to the agency.

FACULTY:

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FDA Regulation of Laboratory-Developed Tests

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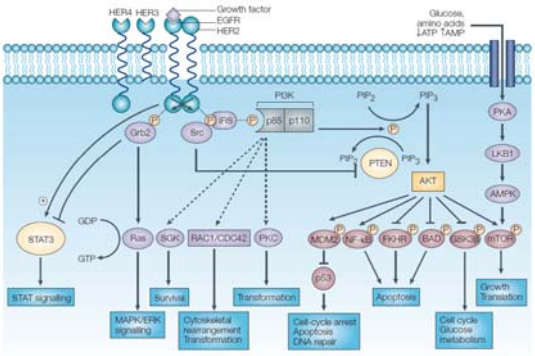
FDA Regulation of Laboratory Developed Tests: Perpectives from a Pathogist Working in the IVD Industry

Kenneth Emancipator, MD, FASCP

Need for FDA Regulation

- LDT's have become an "end run" around FDA as a means of commercializing of novel biomarkers
- Threat to traditional IVD manufacturers ("it's not a level playing field")
  - Limits ability of local laboratories to offer the test
  - Threatens quality of testing if reagents, instruments, and software are not subject to GMP's
- Erosion of the clinician-pathologist-patient relationship
- Practice of Aristotelian science

Signaling Pathways



Pitfalls to FDA Regulation

- Slow … slow … slow …
- Inconsistent decisions
- No way to ensure that FDA will have the ***sustained*** adequate resources it needs to do the job
- FDA often sets the bar too high
  - Especially with regard to clinical validation
  - Sometimes with regard to analytical validation

Pitfalls to FDA Regulation

- A select few become the arbiters of the weight of scientific evidence
- Too much emphasis on avoiding mistakes as opposed to balancing risks with benefits
  - "We don't approve devices that are not safe and effective. Bottom line."
  - One third of emergency appendectomies come out cold

Pitfalls to FDA Regulation

- Danger of further eroding the clinician-pathologist-patient relationship !!!
  - Will the device label replace the pathology consultation?
- Fails to address the qualifications of personnel performing the test
  - Too politically charged?
  - What about the duty to protect public health?

LDT's have provided important stop-gap measures…

- LDT's for H1N1 influenza were offered during the 2009 outbreak, long before diagnostic kits were available by the Emergency Use Authorization
- LDT's for CYP2C19 report all alleles mentioned in the black box warning for Plavix, whereas IVD-labeled kits do not
- Access to CYP2C9 testing via LDT's when added to warfarin label

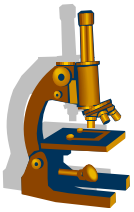
Conflicting Decisions from FDA…

- Plavix label
  - CYP2C19*1 allele corresponds to fully functional metabolism
  - CYP2C19*2 and *3 alleles are nonfunctional
  - Other alleles associated with absent or reduced metabolism are … CYP2C19*4, *5, *6, *7, and *8
- No FDA-cleared device to assay for CYP2C19*4, *5, *6, *7, and *8

Evolution of Clinical Evidence

- Makes sense based on basic science research (clinical hypothesis generation)
- Accumulate anecdotal evidence in favor of hypothesis ("it seems to work")
- Confirm clinical hypothesis via case-control studies
- Validate clinical hypothesis via prospective, randomized clinical trials

Analytical Validation vs Clinical Validation



Dealing with FDA can be frustrating: Example #1

- The following is a direct quote from FDA:

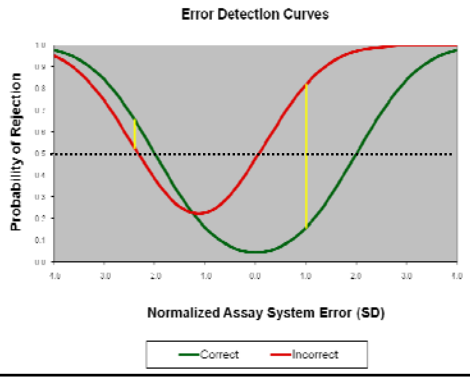
  "As the sensitivity to each of the coagulation factors is too high (>50%), [Device Name] results in normal individuals may yield an abnormal INR/PT (i.e., above the upper limit of the normal reference range) and unnecessary prescription use of oral anticoagulant."

- The labeled indications for warfarin include:
  - Mechanical heart valve replacement
  - Atrial fibrillation
  - Venous thrombosis
  - Pulmonary embolism
  - Myocardial infarction
- **How can a falsely elevated INR/PT possibly lead to unnecessary use of oral anticoagulant?**

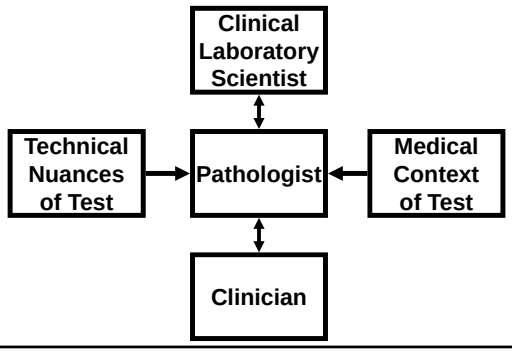
Dealing with FDA can be frustrating: Example #2

- Manufacturer mis-assigned control values
- Controls are intended to be used with a professional use device, i.e. ***not*** CLIA Waived
- FDA's Office of Compliance "requests" full explanation of impact of mis-assignment in recall letter
- Manufacturer includes power curves in recall letter
- FDA's comment: "***They*** won't understand that."

Dealing with FDA can be Frustrating: Example #2



The Traditional Role of the Clinical Pathologist



Public Health Service's Influence on Laboratory Medicine

- Removed professional component (Part B) of reimbursement from most clinical laboratory tests
- Provided safe harbors to Stark Rules that reward clinicians for ordering & performing tests, via Part B reimbursements that remain
- Allows any physician to be the "medical director" of a clinical laboratory (CLIA '88)
- Failed to require licensure for laboratory professionals
- Restricts pathologists' ability to decide what tests need to be offered in his/her practice ???

The Mindset of a Regulator

"In this era of ever increasing complexity in laboratory medicine, clinicians cannot reasonably be expected to be well versed in the nuance of laboratory test selection and interpretation."

Diedre Astin
Director, Clinical Laboratory Evaluation Program
New York State Department of Health

Alternative to FDA Regulation

- Strengthen the clinician-pathologist-patient relationship
- Create incentives for material participation of the pathologist in the development, ordering, and interpretation of LDT's
- The clinician-FDA-patient relationship will not work as well!

Practice of Pathology Versus Manufacture of Diagnostic Test

- Pathologist is materially involved in the development of the test
- Test is offered exclusively to patients within the medical system in which the pathologist has practice privileges
- Pathologist's involvement significantly mitigates the risk of the test
- Laboratory accepts specimens from outside the medical system in which it operates
- Laboratory begins to advertise and promote the test
- Communication between the pathologist and ordering physician is ad hoc, at best

Code of Federal Regulations Title 21

Sec. 807.65 Exemptions for device establishments.

The following classes of persons are exempt from registration …

…

(d) Licensed practitioners, including physicians, dentists, and optometrists, who manufacture or otherwise alter devices solely for use in their practice.

ASCP's Position

- Favors "appropriate regulation"
- Must allow time for current LDT's to continue to be offered, pending FDA submission and clearance or approval
- Favors review by independent party other than FDA, and other than laboratory accrediting agencies

Personal Plea

- Differentiate between LDT's offered "locally" primarily as part of the practice of pathology, and those offered as part of a commercial venture
- Recognize the significant risk mitigation associated with tests offered locally
- Recognize the significant risk mitigation associated with the material participation of board certified pathologists
- Recognize the significant risk mitigation associated with the material participation of ASCP certified clinical laboratory scientists

FDA Oversight of LDTs: Where Are We, and Where Are We Going?

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FDA Regulation of Medical Devices

- 1976 Device Amendments modified the Act to provide for the regulation of Medical Devices
  - Medical Devices: "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent or similar related article. . . intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals" (FFDCA 201(h))

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Definition of IVDs

- IVDs are a subset of medical devices which are "**reagents, instruments, and systems** intended for use in the **diagnosis of disease or other conditions**, including a determination of the state of health, in order to cure, **mitigate, treat, or prevent disease or its sequelae**" (21 CFR 809.3)

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Standard

- Safety
  - There is reasonable assurance. . . That the probable benefits. . . Outweigh any probable risks. [21 CFR 860.7(d)(1)]
- Effectiveness
  - There is reasonable assurance that. . . The use of the device. . . Will provide clinically significant results. [21 CFR 860.7(e)(1)]

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Risk-Based Classification of IVDs

- The risk of an IVD is based on the consequences of a false result
- 3 Classification levels
  - Class I: **common, low risk devices**
  - Class II: **more complex, moderate risk**
  - Class III: **most complex, high risk and novel intended uses**

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Class I IVDs

- Represent common, low-risk devices
  Examples:
  - lactic acid
  - erythrocyte sedimentation rate test
  - differential culture media
- Most exempt from premarket submission
- General Controls are required

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General Controls

- Applicable to medical devices, regardless of class
- Registration and listing
- Good Manufacturing Practices (GMP)
- Reporting of Adverse Events and Recalls
- Device Labeling Provisions
  - Prohibition against misbranding, adulteration, false or misleading claims, sales of banned devices
- Maintenance of Records and Provision of reports to FDA

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Class II IVDs

- Moderate risk devices, tend to be more complex
- Examples:
  - factor deficiency test
  - antimicrobial susceptibility test systems
  - thyroid stimulating hormone test system
- Premarket Notification [510(k)]
- Special Controls
- General Controls

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Special Controls

- What they are:
  - Special requirements for devices when the general controls alone are insufficient
  - May include:
    - special labeling requirements
    - mandatory performance standards
    - postmarket surveillance
- Special controls are described through guidance documents which are posted on FDA's website

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Class III IVDs

- Represent highest risk, most complex devices, novel intended uses

  Examples:
  - Hepatitis B and C, HPV tests
  - Total PSA for prostate cancer screening
  - Continuous Glucose Monitoring Devices
- Premarket Application [PMA]
- Submissions often include clinical data

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Elements of FDA Premarket Review

- Analytical validity
  - Correctly detects analyte
- Clinical validity
  - Correctly identifies disease/condition
- Labeling

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Analytical Performance

- Accuracy
- Precision
- Specificity
- Limits of detection/measurement

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Clinical Performance

- Yardstick of truth – can signals can be turned in to clinical action
- Clinical sensitivity
- Clinical specificity
- Predictive values

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Regulatory Flexibility

- Process is malleable
- Review experience – focused claims
- Transparency – web posting of review templates
- Guidances

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Program Implementation

- Premarket: Industry provides the evidence, FDA reviews and clears or approves
- Postmarket: Industry's responsibility, FDA monitors and provides guidance
- Compliance: FDA monitors companies to make sure they comply with the law and and regulations

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History: LDTs - Then

- Local
- Mostly non-commercial
- Test methods generally well established, accessible
- Clinician/Pathologist/Patient relationships
- Simple software – calculations

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History: LDTs - Then

- Tests usually for diagnosis or monitoring
- Often for rare diseases, unmet needs
- Performed by specialists with advanced training and require expert interpretation (karyotype, IHC)
- Small test volumes

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Enforcement Discretion:

- **Definition:** When FDA does not enforce some or all applicable laws and regulations on certain categories of products (drugs, devices, biologics, etc.)
- Key Points:
  - •Enforcement discretion not unique to LDTs
  - •Enforcement discretion does not change the fact that the law applies
  - •Many different reasons for this practice (risk, history, timing, resources, etc.)
  - •Practices like this do occur, but may change (often because of changes in risk profile of the products)

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Result of Enforcement Discretion

- Enforcement discretion became a loophole
  - – Many LDTs now dependent on components assembled and marketed by others
  - – Business models leverage enforcement discretion for rapid market access, avoid FDA oversight
  - – Parallel industry with traditional IVD manufacturers

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LDTs Now

- Many are the same
- Still often for unmet needs, rare diseases
- Still need for expert interpretation (IHC, cytogenetics, culture, etc.)

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But Also Much More

- Volume and types of LDTs has grown significantly
- Often a mechanism for market entry of novel tests
- Higher proportion in commercial labs and biotechnology companies
- Often no clinician/pathologist/patient relationship
- Tests developed for broad, commercial use

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And …

- Often require complex software
- Many incorporate automated interpretation
- Tests increasingly empirical, non-transparent
- Rely on complex statistical methods
- Clinical validity not well understood
- More tests for predicting drug response, risk of disease
- Novel tests often developed by companies and “licensed” to a lab

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And More

- Tests broadly advertised
- Aggressively marketed to clinicians
- DTC advertising
- Internet sales, overnight shipping
- Nationwide, international reach

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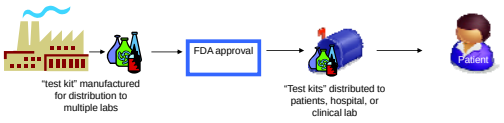
Lab Developed Tests

1) Commercially Distributed Test Pathway:



"test kit" manufactured for distribution to multiple labs

"Test kits" distributed to patients, hospital, or clinical lab

2) Lab Developed Test (LDT) Pathway:

Test designed, manufactured, and used in a single lab

LDTs (lab developed tests) enter the market without review

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IVDs – Two Regulatory Paths

	CLIA	FDA
Research Phase	No	Yes
Analytical validation	Post hoc sampling	Yes
Clinical validation	No	Yes
Report Adverse Events	No requirement; no system	Yes
Transparent Results	No public information	Published review summary

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Risk of Insufficient Oversight

- Tests without sufficient oversight can lead to incorrect diagnoses and/or treatment
- FDA has observed the following in LDTs in recent years:
  - Poor Clinical Validation
  - Faulty Data analysis
  - Exaggerated clinical claims
  - Fraudulent data
  - No post market surveillance
  - Use of Investigational-Stage Devices without Informed Consent

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Benefits of FDA Oversight

- Independent Premarket Review
  - Independent assessment occurs prior to clinical use of test
  - Ensures test limitations are described
  - Ensures test performance claims are supported
- Clinical Validation
  - Provide assurances that test provides clinically meaningful results.
- Post Market Surveillance
  - Mechanism to assist manufacturers and FDA in identifying problems with tests
- Oversight of Investigational-Stage Devices
  - Ensures patients and physicians understand the scientific evidence supporting use of a diagnostic test

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Initial FDA Approach

- Long-running discussion on need for oversight of LDTs
  - SACGHS and other recommendations for oversight in last 10-15 yrs
- Piecemeal approach
  - ASR
  - IVDMIA

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Challenges faced by Historical FDA Approaches

- ASR Rule
  - ASR manufacturers misinterpreted the regulation and sold complete tests inappropriately as ASRs
  - ASR Q&A Guidance (2007) clarified the boundaries of ASRs and the responsibilities of ASR manufacturers
  - Enforcement of the ASR regulations started a resurgence of platforms and tests sold for clinical use but labeled "For Research Use Only" (RUO)
  - RUO tests and instruments of uncertain quality – same situation as early 1990s

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Challenges faced by Historical FDA Approaches

- IVDMIAs:
  - IVDMIAs are complex, non-transparent and difficult to develop and validate correctly
  - FDA stated that FDA premarket review and postmarket surveillance/reporting are necessary to ensure the public is protected from unsafe or inaccurate tests
  - IVDMIA draft guidance stated that these devices should be subject to FDA regulation rather than enforcement discretion, even when offered as LDTs
  - Publication of the IVDMIA guidance generated some controversy. FDA obtained significant public comment on both drafts of the guidance. One issue identified was the difficulty in defining exactly what an IVDMIA was.

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Current FDA Approach for LDTs

- Framework to encompass ALL LDTs
- Develop a framework to close regulatory gaps
  - Public meeting to initiate stakeholder input
  - Elicit proposals through public meeting docket
  - Meet with interested stakeholders

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Possible LDT Exceptions

- Rare Disease LDTs
  - What is “rare”?
    - Currently, HDE for <4000 patients tested
  - Continued enforcement discretion?
  - Minimal phased-in requirements?
- Biothreat, emerging infectious agents
  - Model EUA (if no emergency)
- Traditional LDTs?
  - Need to know who is offering what

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Elements that may be helpful

- Resource management
- Risk-base phase in over time to allow for predictability, planning
- Coordinate with NIH's Genetic Test Registry
- Implement modifications to current oversight structure where appropriate
- Pilot 3rd party reviews and inspections

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What's Next?

- Develop oversight plan
- Publish draft guidances
  - General requirements
  - Information on complying
- Continue stakeholder interaction

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- Thanks!

Regulatory Affairs 101

Kenneth Emancipator, MD, FASCP

Determine Regulatory Path

- 510(k) Exempt
- Class I Reserved
- Traditional 510(k)
  - Special 510(k)
  - Abbreviated 510(k)
- *de novo* 510(k)
- Premarket Approval (PMA)

The “Pre-IDE”

- A very informal process
- No user fee (yet)
- Non-binding on FDA or sponsor
- No statutory requirement for FDA to respond within a certain time
- Reduces clearance or approval time for a device

Tips for Pre-IDE Submissions

- Start process as early as possible
  - May take a while for FDA to respond
  - Probably will take even longer as FDA sees more submissions
  - May take more than one iteration
- Submit entire V&V plan
  - Many sponsors use only for clinical validation plans, only to discover later that they omitted necessary verification studies

Design Controls

Subpart C--Design Controls

Sec. 820.30 Design controls.

(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 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 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 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 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 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 requirements of this part.

Quality Management System

A manufacturer must develop a Quality Management System (QMS) commensurate with:

- risk presented by the device
- complexity of device and manufacturing processes
- size and complexity of organization

Source: Kimberly A. Trautman, FDA

Design Control

Manufacturer vs Laboratory

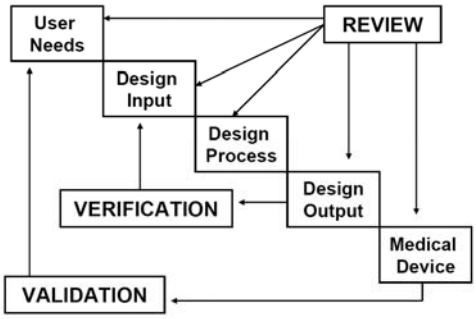
IVD Industry
- World wide company
- Entire installed base of instruments
- All qualified laboratory personnel, world-wide
- R&D to Manufacturing
- Far-removed from end-user

Hospital Core Lab
- One laboratory
- Instrument(s) in one laboratory
- Personnel in one laboratory
- One laboratory
- Close proximity to end-user

Design Controls

a) General
b) Design and Development Planning
c) Design Input
d) Design Output
e) Design Reviews
f) Design Verification
g) Design Validation
h) Design Transfer
i) Design Changes
j) Design History File

Design and Development



Source: Kimberly A. Trautman, FDA

Design Control in the IVD Industry

Requirement	Activity
Design Input	Market Research → Specifications
Design Output	Package Insert Claims
Verification	In-house Studies
Validation	Clinical Trials

The "V&V" Plan in the IVD Industry

- Verification
  - Limit of detection
  - Repeatability (precision)
  - Linearity
  - Bias
- Validation
  - Clinical outcome studies ("high risk" tests)
  - Method comparison at three sites
  - Reproducibility (precision) at three sites

Validation of a Laboratory Developed Test

- "User" of the device is the clinician and/or the patient
- Most LDT's will be considered "high risk" by FDA
- Therefore…
  probably requires *clinical validation*
  - Objective measure of outcome
  - Literature references ???

Tips for Design Control

- “Technical feasibility” may be done before beginning the design control process
- A thorough job during the technical feasibility phase can simplify design control considerably