Validation

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Objectives

- Describe the purpose of validation and its implications as it applies to blood bank automation
- Provide regulatory guidelines for validation
- Explain the process and execution of validation including the stakeholders
- Describe pitfalls to avoid during validation

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Purpose of Validation

- The purpose of validation is to establish documented evidence, which provides a high degree of assurance that a specific process will consistently produce an outcome meeting its predetermined specifications and quality attributes.

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Purpose of Validation

- Manufacturer's Responsibility
  - FDA clearance
- Facility's Responsibility
  - Acceptable Performance on site
    - patient population
    - Geography
    - operating conditions

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Review regulatory and accrediting agencies' requirements

- U.S.
  - FDA
- Other Countries' requirements (CE, ISO)
- State and Local government
- Other agencies
  - AABB
  - CAP
  - COLA
  - Joint Commission

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FDA Validation Regulations

- Code of Federal Regulations
- Title 21 – Food and Drugs
  - Chapter 1 – cGMPs
    - Current Good Manufacturing Practices
- Title 42 – Public Health
  - Part 493 – Laboratory Requirements

Electronic Code of Federal Regulations
e-CFR™

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AABB Standards Requirements

- BBTS 3.2 Qualification of Equipment*
  - All equipment shall be qualified for its intended use, including FDA-cleared or approved devices
    - 3.2.1 Installation Qualification (IQ)
    - 3.2.2 Operational Qualification (OQ)
    - 3.2.3 Performance Qualification (PQ)

*BBTS Standards, 29th Edition, 2014

College of American Pathologists (CAP) Requirements

ALL COMMON CHECKLIST:

- **COM.30550**
  Instrument /Equipment Performance Verification

- **COM.40000**
  There is a summary statement, signed by the laboratory director (or designee who meets CAP director qualifications), documenting review of validation studies and approval of each test for clinical use
- **COM.40300**
  Analytic Accuracy/Precision

- **COM.40400**
  Analytic Sensitivity

- **COM.40500**
  Analytic Interferences

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The Validation Process

- The process should include:
  - Writing a plan
  - Approving the plan
  - Executing the plan
  - Final review/acceptance
  - Implementation

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Writing the plan

- Define the validation process
- Understand and document the manufacturer's
  - Specifications
  - Limitations
    - Package inserts
    - Operator Manual
    - Training materials

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Specifications and Limitations: Examples

- Expected results
  - IgM/IgG
- Hemolysis tolerance
- Sample types
- Turn around time
- Sensitivity/Specificity

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Writing the plan

- A well-written validation plan will answer the questions:
  - Who will be involved?
  - What is being validated?
  - When will it be validated?
  - How is it being validated?

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Who will be involved?

- Facility's own SOP's
- Facility and Vendor Information
  - Names, addresses, phone/fax numbers, contact persons
- Responsibilities
  - Who will:
    - Develop the plan
    - Review/Accept the plan
    - Execute the plan
      - » Vendor
      - » Employees
    - Perform final review/sign-off
- Who and what will be affected by the new process

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What is it being validated?

- What components of the system will be evaluated?
  - Test validation
  - SOP validation
  - Interface validation

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When will it be validated and implemented?

- State the timeline for the validation and implementation
  - Each test
  - SOP's
  - Interface
  - Full implementation

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How is it being validated?

- Number and type of specimens to test
- Any unique testing protocols for the system being validated
  - Frozen samples
  - Age of specimens
  - Specimen spin times
  - Adult vs. Pediatric samples
  - Patient samples vs. Unit samples
  - Proficiency or QC material to be used for validation

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How is it being validated?

- Acceptability requirements
  - Failures & exceptions
    - Who
    - Process
- Apply appropriate calculations to determine acceptability
- Calculations should be well documented and traceable

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How is it being validated?

- Three Components of Validation:
  - Installation Qualification (IQ)
  - Operational Qualification (OQ)
  - Performance Qualification (PQ)

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How is it being validated?

- Installation Qualification (IQ)
  - Confirmation that equipment complies with technical specifications, standards, codes and regulations
  - Equipment functions performed and documented with expected results
  - Usually performed by the vendor
    - Plan should address who will perform this

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How is it being validated?

- Operational Qualification (OQ)
  - Confirmation that the system meets all user requirements as intended by the manufacturer
    - Operator training and documentation
    - Assay configurations
    - Assay performance and interpretation
    - Maintenance processes
  - Usually performed by the vendor
    - Plan should address who will perform this

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How is it being validated?

- Performance Qualification (PQ)
  - Confirmation that the system consistently produces acceptable outcomes under routine operating conditions and functions according to laboratory, regulatory, and accrediting agency requirements
  - Developed and performed by the facility
    - Should include routine and non-routine samples
    - Facility must determine the number and types of samples to run

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How is it being validated?

- Performance Qualification (PQ)
  - Usually presented in Test Case scenarios
  - Challenge for a single validation task
    - is the instrument reading the barcode properly?
  - Challenge for multiple associated validation tasks
    - is the instrument consistently performing correct ABO/Rh typing?

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How is it being validated?

- Performance Qualification (PQ) considerations:
  - Hemolyzed, icteric, lipemic samples
  - Expired reagent challenges
  - QC Challenges
  - Sample identification issues (illegible barcodes, manual entry, etc)
  - Carry over studies
  - Accuracy/Precision studies, Sensitivity & Specificity studies
  - Stress loading
  - Turn around times
  - Parallel Testing
  - Abnormal samples (mixed field, etc.)

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How is it being validated?

- Discrepancies
  - Documentation of the discrepancy
  - Determine what is causing the discrepancy
    - Sample
    - Mechanics
    - Test specifications
    - Investigations should be timely
  - How will it be resolved
  - How to determine which results are acceptable
    - Important to define “tie breaker” method

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How is it being validated?

- Freezing and thawing samples for validation:
  - Manufacturer's limitations and expected effects
  - Freeze thaw may affect the reactivity of antibodies
    - Test thawed samples on both new and reference methods to assure reactivity

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How many is enough?

- Facility decision
  - Manufacturers cannot state what is acceptable
- Statistically meaningful
- Room for adjustment
  - Failures
  - Excluded samples

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How many is enough?

- Example:
  - Medical director wants to have a 95% confidence level in results for antibody screens. He wants a minimum of 50 samples run.

	95% Confidence Level	99% Confidence Level
Number of Failures	Sample Size	
0	59	90
1	94	130
2	125	166

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How is it being validated?

- Number of Antibody Specificities

  Example: a facility has written their plan to test 20 antibody positive samples with one example of anti-JK3. They only do 2 antibody work-ups in a month.

- “antibodies representative of those found in the normal patient population”
- Shared specimens
  - Sister facilities
  - Blood Centers/Reference Labs
  - Proficiency or competency testing samples

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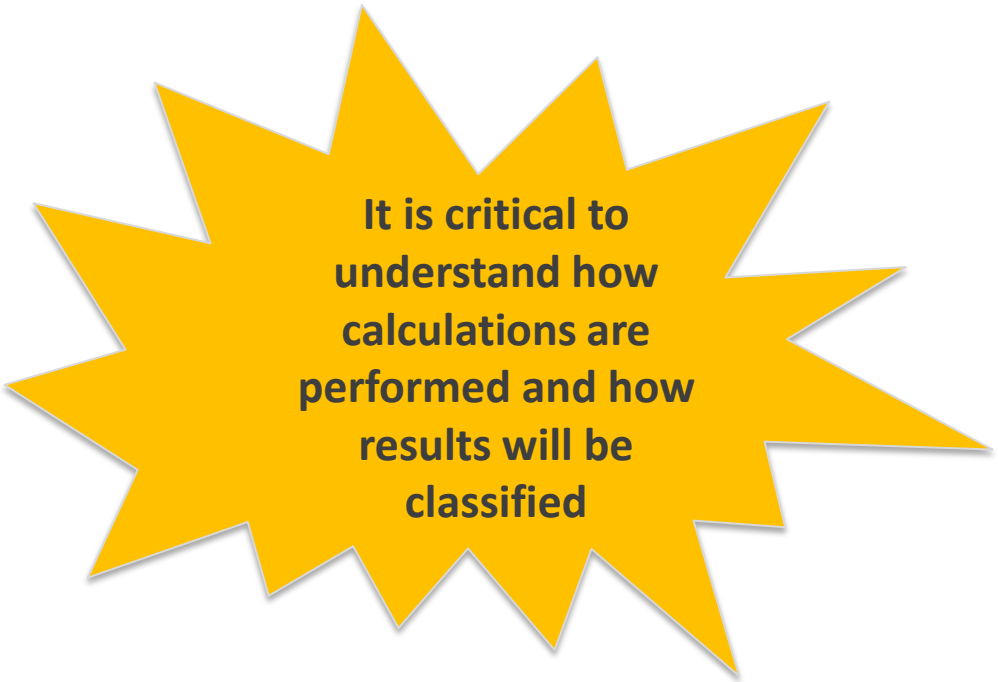
How is it being validated?

- Result definitions
  - True Positive
  - True Negative
  - False Positive
  - False Negative
- Acceptance Criteria
  - Sensitivity
  - Specificity
  - Concordance
  - Accuracy
  - Precision/Reproducibility



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How is it being validated?

- Training
  - Who will be trained and by whom, by what methods?
  - When will competency be assessed?
    - Remember that CLIA requires competency on tests/methods must be assessed before reporting patient results
- Describe conditions which require re-validation

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Approving the plan

- The plan should be approved BEFORE validation begins
  - Review for completeness
  - Assure there is agreement with acceptance criteria
  - Are the test cases in the PQ sufficient ?
  - Helps to assure expectations of those writing the plan and those who will have final sign off on the system are in sync with each other

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Documentation

- Validation records must be maintained (21 CFR 211.68(b), 211.100(b), 606.160(b)(5)(ii))
  - Expected and observed results
  - Interpretation of results as acceptable or unacceptable
  - Corrective action/resolution of unexpected results
  - Explanation of and rationale for any deviation from the validation plan
  - Conclusions and limitations
  - Approval signatures
  - Supporting documentation
  - Implementation timeline

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Final Review/Acceptance

- There should be clear documentation as to:
  - Who performed the final sign-off
  - When the sign-off was done
  - What was signed off

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To recap…

- The validation process should include:
  - Writing a plan
  - Approving the plan
  - Executing the plan
  - Final review/acceptance
  - Implementation of the new system/process

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Final reminder…

- The ultimate responsibility for writing and executing a validation protocol is the facility's responsibility.

- Consider checking with regulatory agencies or peer facilities for criteria that would be acceptable or examples of validation plans.

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References

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