

# Laboratory Quality Control Based on Risk Management

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# Objectives

- Define risk management and its application to clinical laboratory testing
- Understand common sources of error in the laboratory and mechanisms to reduce risk.
- Use the CLSI EP23 document as a resource for developing a quality control plan
- Introduce IQCP from CMS

# Risk Management

- Clinical laboratories conduct a number of activities that could be considered risk management:
  - evaluating the performance of new devices
  - troubleshooting instrument problems (failed QC)
  - responding to physician complaints (POCT doesn't match lab)
  - estimating harm to a patient from incorrect results
  - taking actions to prevent errors (training, QC lockout)
- So, risk management is not a new concept to the laboratory, just a formal term for what we are already doing every day.

# Risk Management Definition

- Systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk (ISO 14971)

# Risk Definition

- Risk – the chance of suffering or encountering harm or loss (Webster's Dictionary and Thesaurus, 1993 Landoll, Ashland, Ohio)
- Risk can be estimated through a combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51)
- Risk essentially is the potential for an error to occur

# Historical Quality Control

- Quality control has historically been utilized to document the stability of an analytical system (environment, operator, and analyzer).
- 1950's industrial model of quality in analytical process – analyze a surrogate sample like a patient sample – called a control, containing known amount of measured analyte.
- If the analytical system can achieve the desired result using the control, then the system is stable and quality products (the patient results) are being produced.

# QC and Systematic Errors

- Systematic errors affect every test in a constant and predictable manner
- Can occur from one point forward or for a limited period of time
- Surrogate sample QC does a good job at detecting systematic errors, like:
  - Reagent deterioration or preparation
  - Improper storage or shipment conditions
  - Incorrect operator technique (dilution, pipette setting)
  - Calibration errors – wrong setpoint, factors

# QC and Random Errors

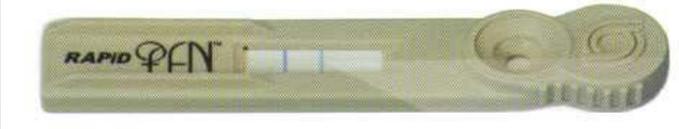
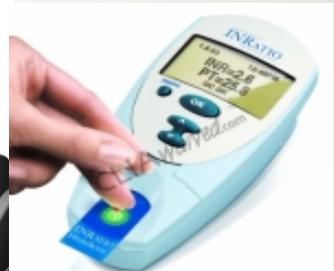
- Errors which affect individual samples in a random and unpredictable fashion, like:
  - Clots
  - Bubbles
  - Interfering substances
- Surrogate sample QC does a poor job at detecting random errors unless the error specifically occurred with the QC sample.

# Quality Control

- A stabilized surrogate sample of known concentration analyzed like a patient sample to determine assay recovery and result stability over time
- Advantages
  - QC has target values, if assay recovers target, then everything is assumed stable (instrument, reagent, operator, sample)
  - QC monitors the end product (result) of the entire test system
- Disadvantages
  - Patients can be reported before problem detected (continuous analyzer)
  - When problem detected must go back and reanalyze patients since last “good” QC
  - For unit-use devices, QC consumes the test and doesn’t ensure next kit
  - QC can be expensive to perform for low volume/high cost tests
- Need to get to fully automated analyzers that eliminate errors upfront, provides assured quality with every sample
  - Until that time, need a robust QC Plan to ensure result quality

# Types of Quality Control

- “On-Board” or Analyzer QC – built in device controls or system checks (IL GEM, Radiometer ABL80, i-stat)
- Internal QC – laboratory analyzed surrogate sample controls. (Manufacturer controls performed on kit)
- External QC – blind proficiency survey, samples sent a few times a year to grade an individual laboratory’s performance against other labs (CAP or Wisconsin State)
- Other types of QC – Control processes either engineered by manufacturer or enacted by laboratory to ensure result reliability (checking temperature indicator in shipping container on receipt of new reagents)



# Manufacturer Checks – Device Built-In or On-Board QC

- Some devices have internal checks which are performed automatically with every specimen:
  - Development of a line (Pregnancy test, Occult blood)
  - Sensor signal (blood gas analyzer, clots)
  - Flow resistance and liquid sensors (clots or bubbles in analyzer pipettes)
- Other checks engineered into device:
  - Temperature indicator in shipping carton
  - Barcoding of reagent expiration dates (prevents use)
  - Lockout features that require successful QC
  - Disposable analyzer cuvettes/pipette tips (carry-over)

# Quality Control

- No single quality control procedure can cover all devices, since devices may differ in design, technology, function, and intended use.
- QC practices developed over the years have provided labs with some degree of assurance that results are valid.
- Newer devices have built-in electronic controls, and “on-board” chemical and biological controls.
- Quality control information from the manufacturer increases the user’s understanding of device overall quality assurance requirements so that informed decisions can be made regarding suitable control procedures.

ISO 15198:2004 Clinical laboratory medicine: *In vitro* diagnostic medical devices – Validation of user quality control procedures by the manufacturer.

# Lab-Manufacturer Partnership

- Developing a quality plan surrounding a laboratory device requires a partnership between the manufacturer and the laboratory
- Some sources of error may be detected automatically by the device and prevented, while others may require the laboratory to do something, like analyze external QC on receipt of new lots of reagents.
- Clear communication of potential sources of error and delineation of lab and manufacturer roles for how to detect and prevent those risks.

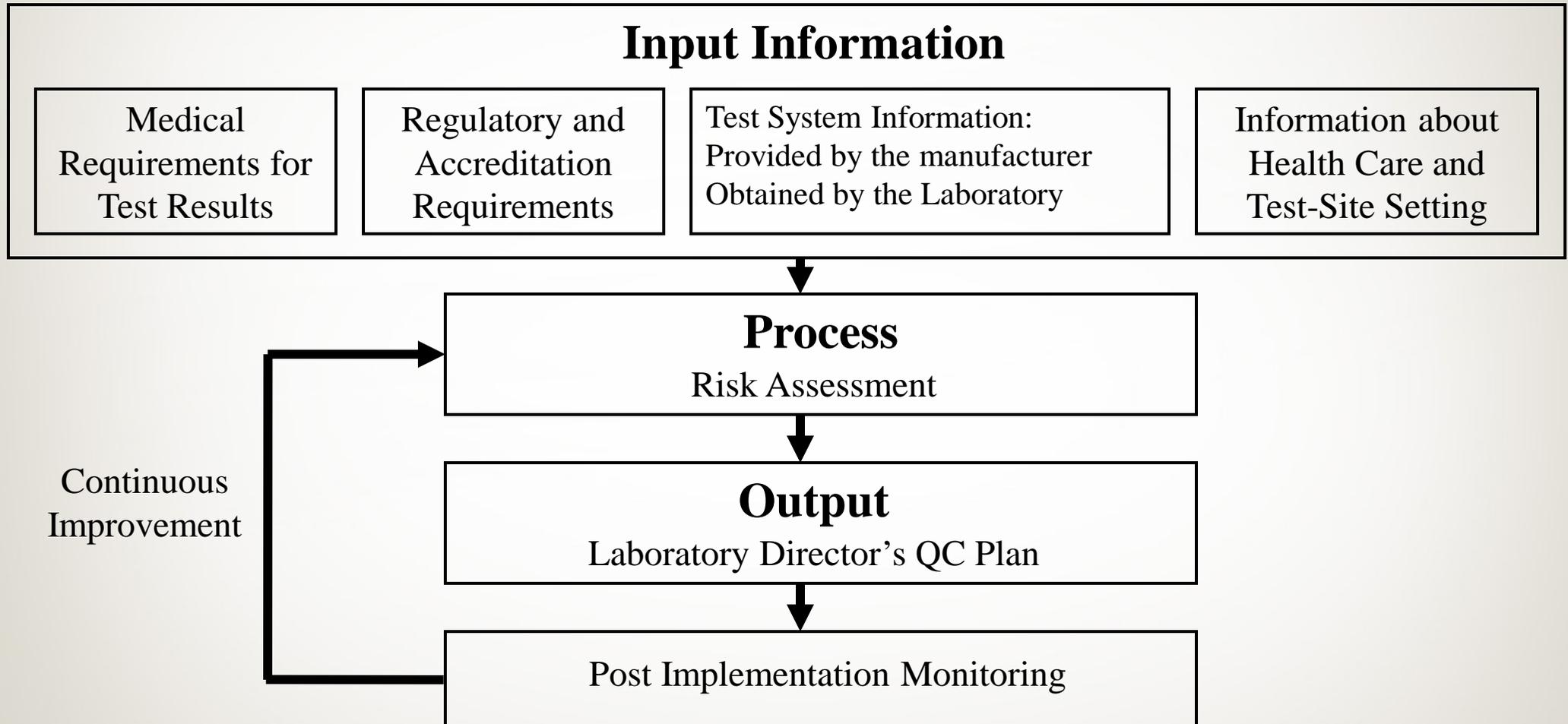
# CLSI Project: EP23

- Laboratory Quality Control Based on Risk Management.
- James H. Nichols, Ph.D., Chairholder
- EP23 describes good laboratory practice for developing a quality control plan based on manufacturer's information, applicable regulatory and accreditation requirements, and the individual healthcare and laboratory setting

# CLSI EP23

- CLSI EP23 provides guidance on developing an appropriate QCP that will:
  - Save time and money.
  - Use electronic and/or integrated QC features.
  - Use other sources of QC information.
  - Conform to one's laboratory and clinical use of the test.

# EP23 Laboratory QC Based on Risk Management



# Developing a Quality Control Plan

- Where to start?
- How does a laboratory develop a Quality Control Plan?

# Developing a QC Plan A Rapid Serum hCG Test

## Collecting Information about the Test

# Laboratory Example

## A Rapid Serum hCG Test

- Generic serum hCG test in a physician office practice
- Low volume 0–2 tests/day
- Need for daily liquid QC uses 2 kits (\$20 ea) and adds 20 mins TAT.
- Adoption of nontraditional QC through EP23 would improve cost, test and labor efficiency.



# Rapid Serum hCG Test Kit

- Test device
  - Polyclonal mouse anti- $\alpha$  hCG coated membrane (test line)
  - Pad with monoclonal mouse anti- $\beta$  hCG colored conjugate
  - Goat anti-mouse coated membrane (control line)
- Disposable dropper for sample transfer
- Packaged in foil pouch



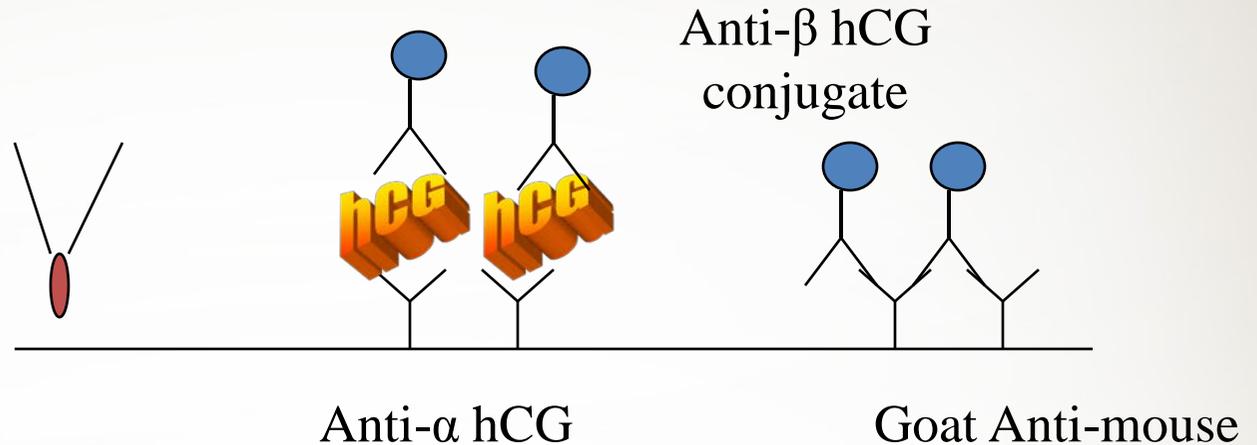
# Rapid Serum hCG Test

- Solid phase, two-site, immunochromatography or immunometric assay
  - Sample added to well with pipette
  - hCG positive – sample reacts with colored conjugate-mouse anti- $\beta$  hCG antibody
  - hCG bound conjugate binds to anti- $\alpha$  antibody at test line
  - Conjugate binds to goat anti mouse antibody on membrane to generate a control line
  - Control line – separate antibody-conjugate
  - 2 lines = positive
  - 1 line at control = negative

# Two-Site Immunometric Assays

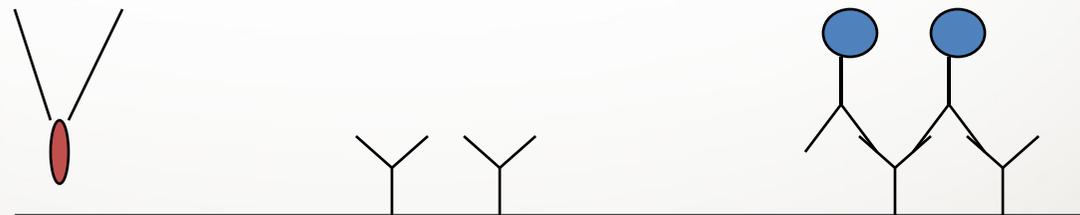
Positive

2 lines

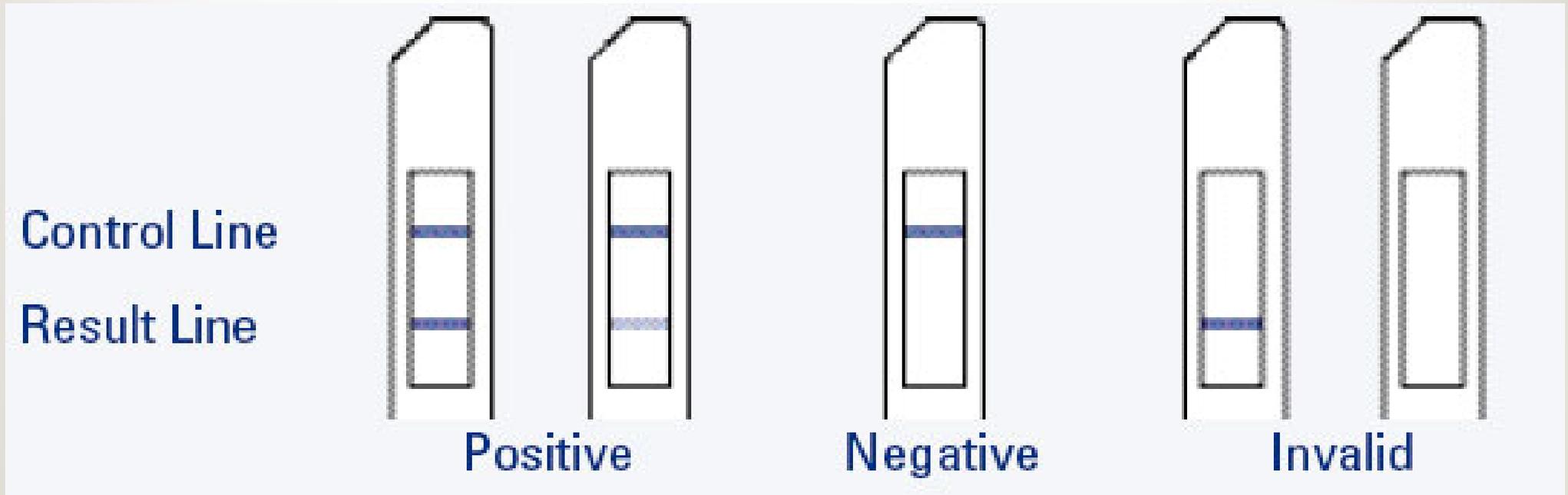


Negative

1 line



# Rapid Serum hCG Test Interpretation



# hCG Internal Control Processes

- Internal procedural control line verifies:
  - Sample and reagent wicking on membrane
  - Adequate sample volume
  - Reagents viability - control/test lines/conjugate color reactive
  - Correct procedure
- Internal negative procedural control:
  - Background clearing – to clear and read lines
  - Adequate wicking

# Package Insert QC Recommendations for Rapid Serum hCG Test

- Internal QC:
  - Verify internal positive control line with each test
  - Ensure background clears on each test to adequately read test line (negative control)
- External Liquid QC:
  - With each new lot
  - Each shipment
  - As required by federal, state, or local regulations
  - To verify reactivity of reagents whenever a doubt
  - (Note external QC with each box is not recommended)

# Liquid Quality Control Frequency

- Minimum – follow manufacturer recommendations and regulatory requirements (CLIA moderate complex testing – two levels q24 hrs)
- Manufacturer recommends liquid QC with each
  - Shipment
  - New lot
  - Whenever question of test system performance
- Options for determining liquid QC frequency
  - Peer publications – verify what others are already doing
  - Develop QC rules based on six-sigma of test system
  - Verify in your facility:
    - analyze 2 levels each day for several weeks, then reduce to every few days for several more weeks, then weekly/monthly after more experience with test system
- Pregnancy testing is manual, no QC-lockout or device features

# Developing a QC Plan A Rapid Serum hCG Test

## Mapping the process to find the weak steps

# Process Map: Finding the Weak Steps in the hCG Process

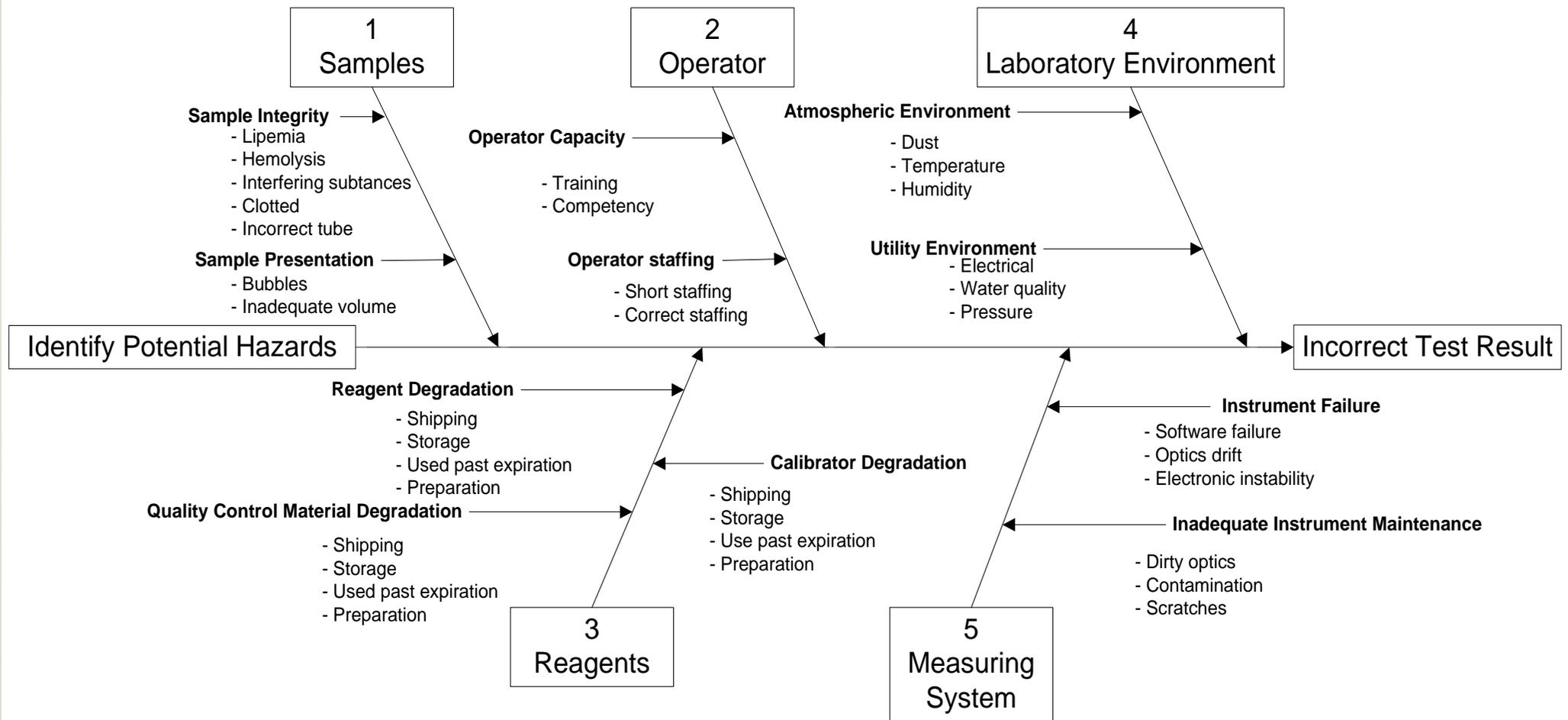
- Work from the current package insert
- Test Order – Electronic or hardcopy
- Test Collection –
  - False + – Patients with human anti-mouse Abs (HAMA), trophoblastic and other neoplasms may cause increased hCG.
  - False - - too early in pregnancy and hCG below detection limit – retest in 48 hrs.
  - Wrong tube type – serum required
  - Sample degradation/processing – delay/temp exposure – hemolysis/clots
- Analysis –
  - Reagent exposure during shipment or degradation during storage
  - Wrong sample volume/bubbles/clots applied to kit
  - Incorrect procedure
  - Incorrect timing
  - Wrong interpretation
- Results – Transcription errors

# Developing a QC Plan A Rapid Serum hCG Test

## Risk Assessment

# Sources of Laboratory Error

- Environmental:
  - Temperature
  - Humidity
  - Light intensity
  - Altitude
- Operator:
  - Improper specimen prep, handling
  - Incorrect test interpretation
  - Failure to follow test system instructions
- Specimen:
  - Bubbles
  - Clots
  - Incorrect tube additive
- Analysis:
  - Calibration factor incorrect
  - Mechanical failure



Fishbone Diagram from CLSI EP23...Refer to Appendix A in CLSI EP18 for more comprehensive list of error sources

# Rapid Serum hCG Test Risk Assessment

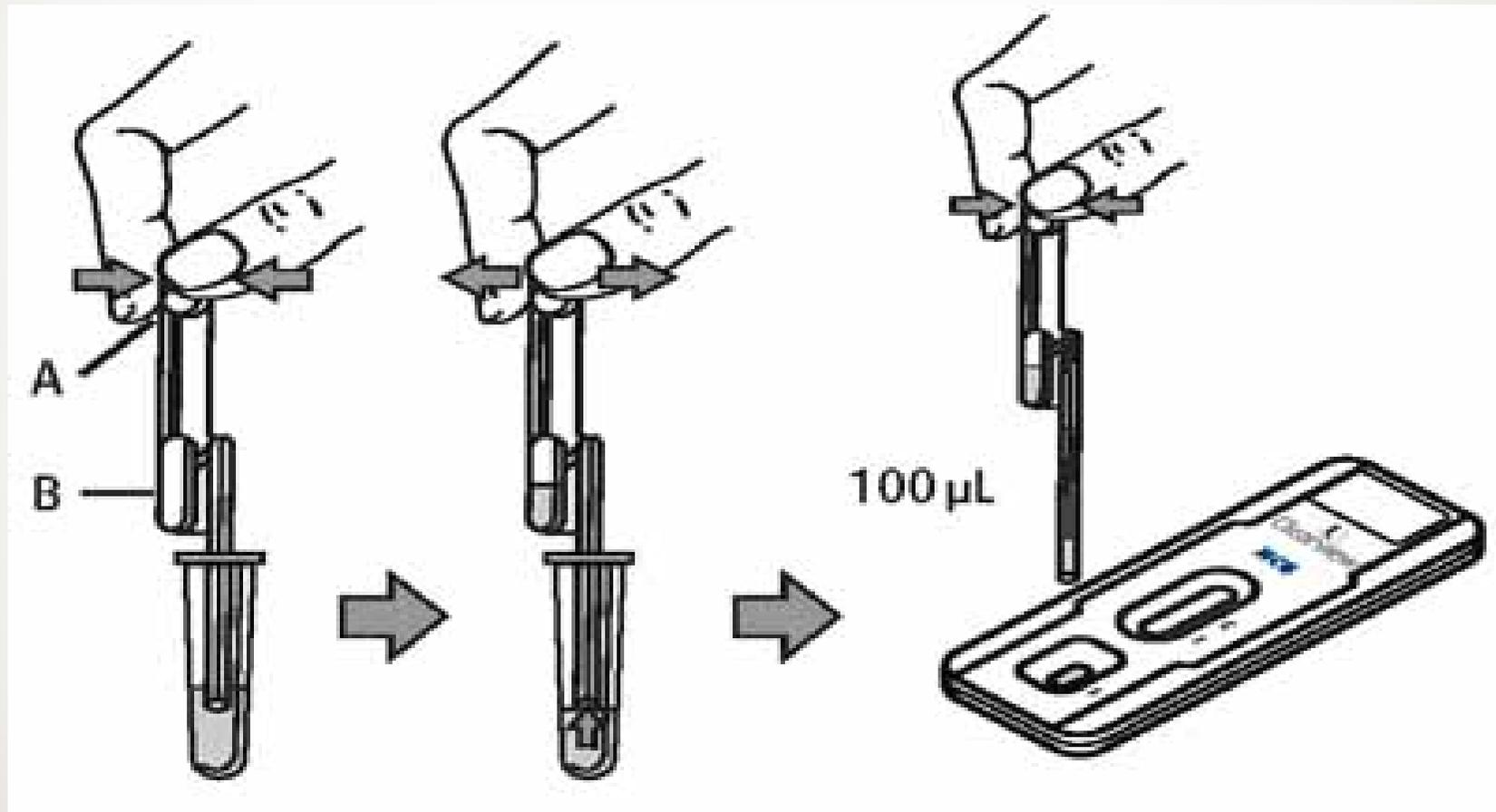
- Samples
  - Wrong tube type – YES this is possible and presents residual risk of error - *train to verify tube before processing*
  - Delays/hemolysis/clot – YES this is possible and presents residual risk of error - *train to process and separate promptly, maintain centrifuges as required*
  - Temp – YES there is residual risk - *thaw tubes min 30 mins to room temp, centrifuge serum to remove particulates or lipidemia*
  - Interferences – YES there is residual risk - *physician education on test limitations HAMA, hCG secreting tumors through EMR, newsletters or test comments*

# Rapid Serum hCG Test

## Risk Assessment

- Operator
  - Expired reagents – YES (residual risk) - reagent reactivity degraded, *internal control will detect, train staff to check dates at use*
  - Incorrect procedure – N/A (residual risk not significant) – bubbles/clots, *test will not flow detected by internal control*
  - Wrong timing – YES (residual risk) – (3 min vs 3-5 min) *use timer/alarm*
  - Erroneous interpretation – YES (residual risk) – *train staff, use cheat sheets (2 lines +, 1 line -), double check results*
  - Transcription error – YES (residual risk) – *double check result reporting*
  - Too much or too little sample application- Minimal residual risk – *internal control will detect, use dedicated pipette*

# Rapid Serum hCG Test



# Rapid Serum hCG Test

## Risk Assessment

- Reagents
  - Test exposure outside specs (temp, humidity, etc) during shipment - YES (residual risk) – *analyze liquid QC with each shipment*
  - Lot to lot variability – YES (residual risk) – *analyze liquid QC with each lot*
  - Degradation during storage – YES (residual risk) - *monitor storage conditions (2 - 30 ° C), bring to room temp at least 30 mins before use ... analyze liquid QC monthly (based on lab established stability)*
  - Liquid QC degradation – YES (residual risk) *monitor refrigerator (2 - 8 ° C), bring to room temp at least 30 mins before use, discard w/i 30 days of opening bottle*

# Rapid Serum hCG Test Risk Assessment

- Environment
  - Light – YES – *keep kits in foil pouch until use, interpret results under adequate lighting*
  - Physician Office – Minimal - *no prior issues with other testing noted at this location*
- Clinical Application
  - Immediate medical decisions – YES *internal control checked with each test, encourage retest if result doesn't match patient condition*
  - Stability of sample – N/A *sample stable room temp, refrigerated or frozen for retest*

# Developing a QC Plan

## A Rapid Serum hCG Test

# The QC Plan

# Rapid Serum hCG Test QC Plan

- Analyze liquid QC
  - Each new shipment\*
  - Start of a new lot\*
  - Monthly (based on lab established stability)
  - Whenever uncertainty about test\*
- Internal controls with each test\*
- Physician education on test limitations
- Use timer for test development in well lit area
- Use dedicated transfer pipette for sample application
- Use checklist to document training/competency
  - Proper tube type and prompt processing (centrifuge maintenance)
  - Check expiration dates before use
  - Bring samples and kits to room temperature before use
  - Proper test interpretation and double-check result reporting
  - Monitor refrigerator and room temp

(\* Manufacturer recommendations)

# Developing a QC Plan A Rapid Serum hCG Test

## Implementing the QC Plan

# QC Plan Implementation

## Rapid Serum hCG Test Quality Monitors

- Liquid QC failure rates
- Frequency test kit failure (internal QC line)
- Number complaints: requests for retest
- Frequency specimen issues – hemolysis, clots or other problem (particulates)
- Any other unexpected error

# QC Plan Implementation

## Rapid Serum hCG Test Quality Monitors

- Test implemented and used for several months without incidence
- Physicians pleased with TAT of results in clinic
- Staff experienced no issue with managing serum testing in quality manner with this particular hCG test
- Issue arose with a different pregnancy test – separate manufacturer, at a neighboring clinic regarding urine hCG test interpretation using a serum/urine combo test.
- Manufacturer claims “ANY” signal in the test area should be interpreted as positive, but on retest using a different manufacturer’s kit, these patients are negative...



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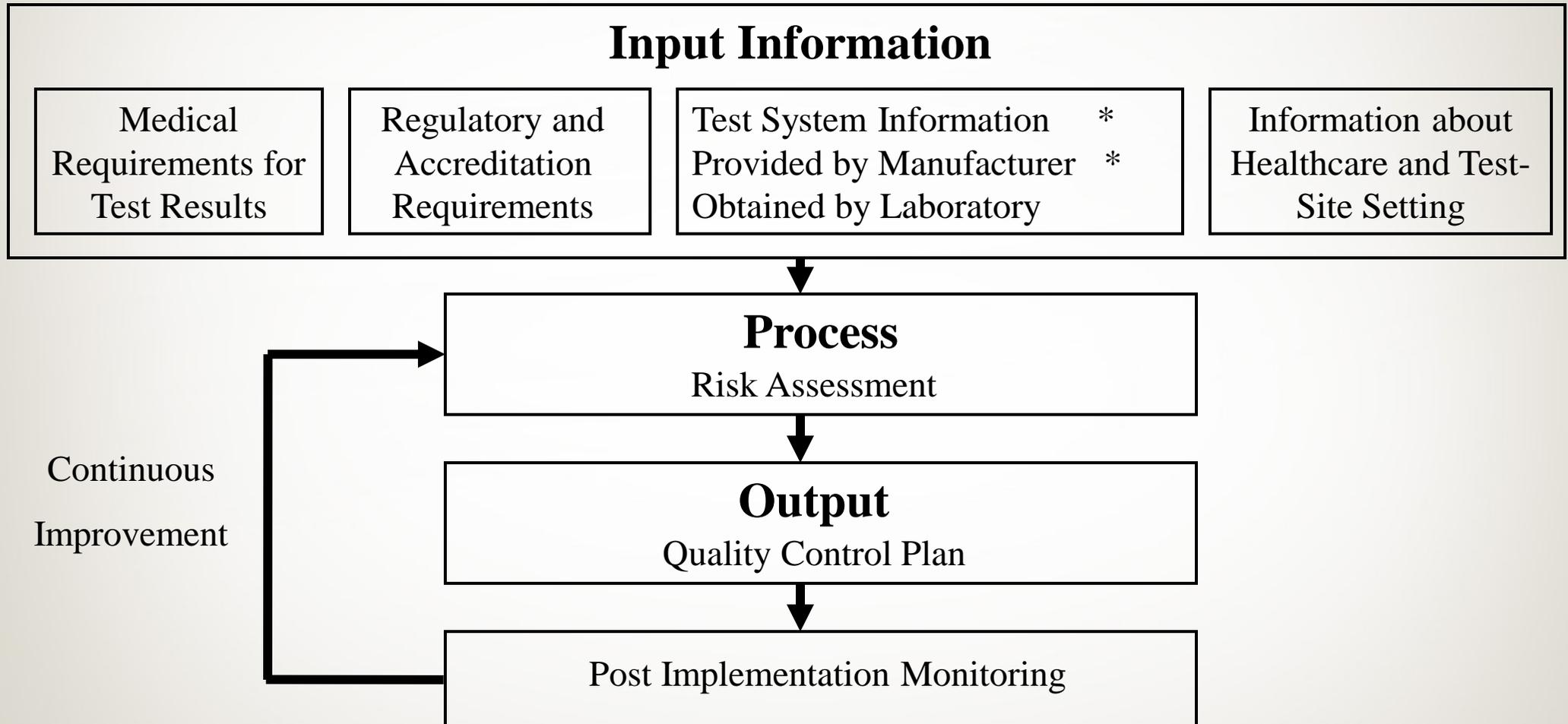


# Rapid hCG Test

## Corrective Action

- Contacted manufacturer – confirmed interpretation of results
- Manufacturer claims this clinic is the only customer to make this complaint
- Saved specimens for retesting on new shipment same lot and different lot - identical results.
- Other negative and positive specimens noted to generate “ghost” like reactivity at test area
- Clinic eventually discontinued using product and switched to a different manufacturer without further incidence. (Site needed to review their QC plan and modify risk assessment based on new product!)

# EP23 Laboratory QC Based on Risk Management



# Risk Management Process

## Life-Cycle Risk Management Process

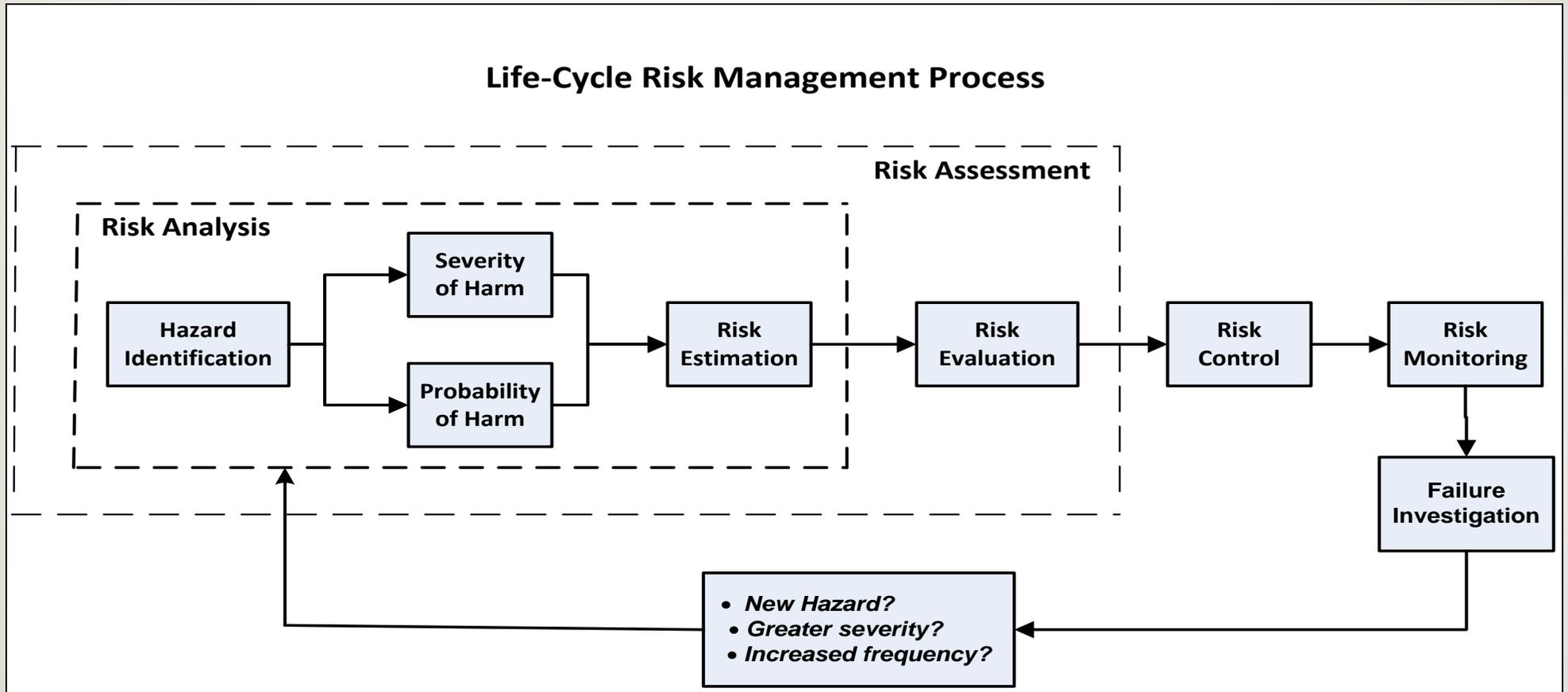


Diagram from CLSI EP23

# EP23 Quality Control Plan

- Risk management allows laboratories to address their specific risks in order of priority
- QC Plan customized for individual lab, medical application of test result, and tolerance for error
- Labs with specific issues (frequent staff turnover) may need additional control processes (like more frequent staff competency checks or education, more frequent QC) than other labs
- **Quality control plan is based on manufacturer recommendations and regulatory requirements, can't reduce frequency of control processes lower than what is required by local law!**
- The laboratory director is the person responsible for test quality and they should be the person to determine how to best ensure quality in their laboratory (ie what control processes to use and at what frequency).
- Once implemented, the quality control plan is monitored for failures and modified as needed to maintain risk to a clinically acceptable level.

# The “Right QC” is IQCP

- CMS will incorporate key EP-23 concepts into CLIA Interpretive Guidelines (IG) as an alternative QC policy called IQCP (Individualized QC Plans)
- Effective Jan 1, 2014, IQCP will supersede the current EQC policy (3 options for decreasing liquid QC frequency)
- Existing CLIA QC & quality system concepts won't change
- No regulations will change!
- CMS' survey process won't change
- 2 year phase-in and educational process

# The “Right QC” is IQCP

- Permits labs to develop an IQCP using many of their existing quality practices/information
- Is based on labs’ patient population, environment, test system, clinical uses, etc.
- Applies to CMS-certified non-waived labs
- IQCP is a choice & default is 2 external QC/day
- Labs must follow mfr’s. instructions if > CLIA
- Includes existing & new analytes/test systems

# Summary

- A quality control plan simply summarizes the risk for potential errors with a device and how the lab intends to address those risks.
- A quality control plan can be high level or very detailed depending on the device, the laboratory, and clinical application of the test result and may vary from one lab to next.
- Risk management and developing QC plans are generally accepted by the industry. Depends on extent to which the device's intended features or actions, achieve its intended purpose in union with the lab's expectation for ensuring quality test results.
- Once implemented, the quality control plan is monitored for effectiveness and modified as needed to maintain risk to an acceptable level.