Developing an Individualized Quality Control Plan (IQCP) For Cepheid's GeneXpert® Diagnostic Systems

BACKGROUND

On January 1, 2014, the Center for Medicare and Medicaid Services (CMS) adopted an alternative Quality Control (QC) procedure that would allow laboratories – after appropriate assessment – the choice to implement a more flexible and customized QC procedure that is better adapted to the needs of their institution[a]. Laboratories have from now until 12/31/15 to design and implement individualized QC plans (IQCP) for tests they believe would benefit from alternative quality control procedures (e.g., less frequent external controls for internally controlled systems). CMS leadership publicly indicated that barring extreme circumstances, CMS would not cite deficiencies to laboratories seeking to implement an IQCP program[b].

Between now and 12/31/15 laboratories can:

1. Continue to follow CLIA requirements as written.
2. Follow Equivalent Quality Control (EQC) procedures. (NOTE: molecular amplification systems were excluded from EQC).
3. Implement IQCP.

Effective 1/1/16, EQC will no longer be available and laboratories will be required to follow either CLIA or IQCP. Also after 1/1/16, laboratories will be cited for deficiencies under IQCP.

Based on CMS' memo from the Survey and Certification Group of State Surveyor Agencies[c], the material that follows may help you should you wish to implement IQCP the GeneXpert menu of assays on the GeneXpert Diagnostic System.

PRINCIPLES OF IQCP

According to CMS.gov, "IQCP considers the entire testing process: pre-analytic, analytic, and post-analytic; thus, your laboratory will need to consider the corresponding risks in each of these phases and applicable regulatory requirements."

The IQCP includes three parts:

1. Risk assessment (RA): identification and evaluation of potential failures and/or errors in a testing process, including:
    a. Specimen
    b. Environment
    c. Reagent
    d. Test System
    e. Testing Personnel
2. Quality Control Plan (QCP): the laboratory's standard operating procedure describing the practices and resources to ensure quality for a test system.
3. Quality Assessment (QA) Plan: the laboratory's policy for monitoring the effectiveness of the IQCP.

The Clinical Laboratory Standards Institute (CLSI) has developed a guideline that provides additional information about risk management: EP-23: Laboratory Quality Control Based on Risk Management; Approved Guideline[d]. IQCP is not the same as EP-23, however, many of the concepts adopted in IQCP were developed as part of the consensus process which adopted EP-23, including representatives from CMS, the Food and Drug Administration, industry and clinical laboratories.

IQCP is a method for laboratories to implement flexible QCPs that evolve with technology. Cepheid's GeneXpert System is a closed in vitro diagnostic assay platform that employs single-use, self-contained Xpert cartridges. As each individual assay is performed, external system and internal cartridge quality control factors check the instrument system, cartridge reagents, on-board sample processing, and presence of favorable reaction conditions for PCR performance. These internal quality control features verify multiple aspects of assay performance for every sample tested.

Many of the other required elements of IQCP (such as monitoring of environmental conditions and training of personnel) may already be documented and will not necessarily require modification, but rather to reference current procedures and document where if necessary modifications are made for a specific test system.

CMS notes that laboratories must follow manufacturer's instructions, particularly where QC frequencies are noted. Performance of external QC is still required upon receipt of new reagent shipments and/or lots, system or software updates, protocol or trend changes, or at the laboratory director's discretion. Cepheid does not provide a manufacturer recommendation for external QC frequency. IQCP may allow your laboratory to reduce external QC frequency if it is determined that a test system's internal controls are sufficient to monitor proper test function, in conjunction with your pre-analytic and post-analytic QC process(es).

NOTE: CLIA specialties of Pathology, Histopathology, Oral Pathology and Cytology are not eligible to use IQCP.

USING THIS DOCUMENT

Cepheid is providing this document as a general information tool only for the GeneXpert Diagnostic System (GX). It is not intended as an endorsement and/or requirement by Cepheid to utilize such a protocol, nor does it apply to assays performed on the SmartCycler. It is the sole responsibility of the laboratory to formulate their specific IQCP. Laboratories using any Xpert assay on the GeneXpert Diagnostic System must read and understand each assay's package insert and instructions for use. Laboratories must comply with local, state and federal rules and regulations.

IQCP SUGGESTED DOCUMENTATION

Aspects of your IQCP may be applicable across multiple Xpert assays. For example, GX instrument operation controls and some internal controls (i.e. probe check and SPC) may be identical for some assays. However, if assays differ in factors potentially leading to error or failure (see below), each assay must be addressed individually.

1.0 RISK ASSESSMENT

1.1 SOURCES OF INFORMATION

- Regulatory requirements
- Manufacturer's package insert
- Manufacturer's operator manual
- Manufacturer's alerts and bulletins
- Verification data or establishment of performance specifications
- Testing personnel qualifications, training, and competency
- QC data and protocols
- Proficiency testing data
- QA documentation, including corrective action
- Scientific publications
- Other information or processes as appropriate

1.2 RISK IDENTIFICATION

The risk assessment is the identification and evaluation of the potential failures and sources of error in a testing process. At minimum, the risk assessment must include evaluation of factors relative to:

- Specimen(s)
  - » Patient preparation
  - » Specimen collection
  - » Specimen labeling
  - » Specimen storage, preservation, and stability
  - » Specimen transportation
  - » Specimen processing
  - » Specimen acceptability and rejection
  - » Specimen referral
- Environment
  - » Temperature
  - » Airflow/ventilation
  - » Light intensity
  - » Noise and vibration
  - » Humidity
  - » Altitude
  - » Dust
  - » Water
  - » Utilities (electrical failure/power supply variance or surge)
  - » Adequate space
  - » Mobility: are instrument(s) transported from one test site to another (mobile lab or hand held devices)
- Reagent(s)
  - » Shipping/receiving
  - » Storage condition requirements
  - » Expiration date(s)
  - » Preparation
  - » External QC (e.g., material, contamination, deterioration, lot variation)
- Test system(s)
  - » Capability to detected interfering substances, inadequate sampling, and other specimen associated issues
  - » Calibration associated issues
  - » Mechanical/electronic failure (e.g., computer, module optics, plunger rod, barcode readers, valve drive motor, etc.)
  - » Failure of system controls and function checks (internal controls, external QC, temperature monitors)

  - » Software/hardware
  - » LIS communication failures
  - » Result reporting
- Testing personnel/operators (on all shifts responsible for performing testing)
  - » Training
  - » Competency
  - » Appropriate education and experience qualifications
  - » Adequate staffing

The assessment must span the entire testing process: pre-analytic, analytic, and post-analytic phases for each factor.

See **Appendix A: Sample Fishbone Diagram for Xpert Testing Process**

1.3 RISK EVALUATION

Once potential errors are identified, the laboratory director must evaluate the potential frequency and impact of the error.

1.4 RISK MITIGATIONS

Once potential errors are identified, the laboratory must demonstrate how internal controls, external controls, and laboratory quality policies and procedures minimize the risk of error.

1.4.1 Internal Controls

For information related to internal control features, refer to **GeneXpert® Quality Control Features for All Cepheid Xpert® Tests.**

1.4.2 External Controls

Describe within your IQCP how your external control policy minimizes the risk of error. For example, you run external controls when:

- Receipt of new shipment(s)
- Receipt of new lot(s)
- Drift in results (e.g., increasing/decreasing positivity rate)
- Suspicious instrument behavior
- Potential contamination (negative control)
- After maintenance and/or Xpert® Check
- Any time a lab director feels is necessary to check operation of the system.

For information related to commercially available external control options, refer to **Xpert® Tests Materials Checklists.**

1.4.3 Training requirements

Describe within your IQCP how your laboratory training and competency program minimizes the risk of error.

1.4.3.1 Manufacturer Training

The Cepheid training program is accredited by the Professional Acknowledgment for Continuing Education (PACE)[e] program. The program is presented in seminar format with a laboratory component at the customer site upon initial installation:

- Infinity (4 hours)
- GeneXpert (3 hours)
- Each Xpert assay (1 hour)

This hands-on training is designed for customers who have purchased any of the FDA-cleared Xpert assays. System training introduces users to basic principles of real-time PCR, GeneXpert Diagnostic System and software function and operation, and internal control strategy. Assay training introduces users to test specific aspects such as sample collection and storage requirements, cartridge preparation, and result interpretation. These concepts and theories are reinforced with hands-on training by testing laboratory provided patient samples.

1.4.3.2 By laboratory (reference/insert laboratory training policies)

Describe how your laboratory ensures that additional operators not trained by Cepheid are competent to perform patient testing. Cepheid provides training materials such as user training PowerPoints, cartridge prep cards, and hands-on checklists that may assist in developing or enhancing your current training protocol.

1.4.4 Proficiency Testing

Describe your laboratory's method of proficiency testing. Several vendors offer proficiency surveys for molecular testing. Common vendors include CAP, API, NY State, and Wisconsin State Laboratory of Public Health. A comprehensive list of CLIA approved PT Providers can be found at http://www.cms.gov/Regulations-and Guidance/Legislation/CLIA/Proficiency_Testing_Providers.html. Note that all CLIA approved PT vendors may not provide surveys compatible with Cepheid Xpert assays.

2.0 INDIVIDUALIZED QUALITY CONTROL PLAN (IQCP)

The IQCP describes the practices, resources and procedures used to control the quality of the testing process. The IQCP will include:

- Identification of risk(s)
- Identification of risk(s) mitigation(s)
- Remaining risk(s) if mitigation(s) is not effective

Appendix B: Sample Risk Assessment for Cepheid GeneXpert Tests(s) is a document that identifies some common sources of potential error associated with the specimen, reagents, test system(s), environment, and operator(s) and includes information about the manufacturer's design features that mitigate risk(s). Laboratories will need to customize fields according to their specific quality assurance practices and procedures. Ultimately, the laboratory director is responsible to ensure the information is truthful and accurate.

3.0 QUALITY ASSESSMENT

Quality Assessment describes the review process for ongoing monitoring of the effectiveness of the IQCP. Items to consider include, but are not limited to:

- QC review/data
- Proficiency testing results
- Patient results review
- Specimen rejection logs
- Turn-around time reports
- Records of preventive measures, corrective actions and follow-up
- Personnel competency records
- Complaints
- Inspection observations
- Investigation of any process failure and follow up activity (modifications as necessary)
- GX system logs, reports, invalid rates, etc.

Much of this material will come from the laboratory's own documentation. For the GeneXpert System, relevant documents may be found in the Operator's Manual, Package Insert, and/or Implementation Guide.

For more information about conducting risk assessment in a laboratory, please see:
CLSI. Laboratory Documents: Laboratory Control Based on Risk Management; Approved Guideline—First Edition. CLSI document EP-23-A1. Wayne, PA: Clinical and Laboratory Standards Institute; 2011.

References

a. Official CMS notifications and materials available at: [http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Individualized_Quality_Control_Plan_IQCP.html]. Accessed May 27, 2014.

b. See presentation at: [http://www.cms.gov/Outreach-and-Education/Outreach/NPC/Downloads/2014-05-19-CLIA-Presentation.PDF]. Accessed May 27, 2014.

c. Available at: [http://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-13-54.pdf]. Accessed May 27, 2014.

d. Available at: [http: www.clsi.org].

e. P.A.C.E.® is an administrative system serving as the quality assurance mechanism for continuing education programs offered to clinical laboratory professionals. Participants in P.A.C.E.® approved educational sessions have confidence in the quality of the program, and receive continuing education contact hours satisfy continuing education requirements for federal regulations, state licensure, certification agencies and employers. For more information, see [http://www.ascls.org/leadership/pace/]. Accessed May 15, 2010.