



## Association for Molecular Pathology

Promoting Clinical Practice, Basic Research, and Education in Molecular Pathology

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May 22, 2006

Mark McClellan, Administrator  
Centers for Medicare and Medicaid Services  
Hubert H. Humphrey Building  
200 Independence Ave., S.W., Rm. 314G  
Washington, DC 20201

Dear Dr. McClellan:

The Association for Molecular Pathology (AMP) would like to provide comments to the Center for Medicare and Medicaid Services (CMS) regarding requirements related to the optimal frequency of performing external quality control (QC) checks for molecular diagnostic laboratory tests.

As background, AMP is a national not-for-profit educational society representing over fourteen hundred physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on nucleic acid technology. AMP members practice their specialty in academic medical centers, independent medical laboratories, community hospitals, federal and state health laboratories, and the *in vitro* diagnostic industry. In this capacity AMP members are involved in every aspect of molecular diagnostic testing, administration and interpretation of molecular diagnostic tests, research and development, and education. For the last several years AMP has provided national leadership for the advancement of safe and effective practice and education for molecular diagnostic testing in the health care industry.

### ISSUE

Currently, molecular technologies (specifically those relying on amplification methods) are excluded from CMS' equivalent QC policy. As a result, there is a lack of consensus between government, industry, and laboratory professionals as to the optimal frequency of running external control materials for molecular testing.

### BACKGROUND

Testing of nucleic acids (DNA or RNA) isolated from patient specimens for the diagnosis of heritable diseases or conditions, genetic variations, or infectious diseases is rapidly becoming a standard of care in laboratory testing. In many cases, molecular diagnostic tests are more sensitive and specific, and have a more rapid turnaround time compared to traditional testing methods. Some examples where molecular testing is the standard of care include diagnosis of herpes simplex virus (HSV) encephalitis, enterovirus (EV) meningitis, monitoring response to antiretroviral therapy in patients infected with human immunodeficiency virus (HIV), and screening for cystic fibrosis in couples of childbearing age. Over the past decade, molecular methods have become more standardized and automated. On March 1, 2006, Cepheid announced that they submitted a 510(k) for FDA review for a point-of-care (POC) molecular test which is intended to be performed in moderate complexity laboratory settings. Cepheid's test detects Group B Streptococcus (GBS) in vaginal-rectal specimens from pregnant women. The GBS test involves minimal handling by the user; the specimen is collected on a swab and the user (e.g. labor and delivery nurse) places the swab in a cartridge which is loaded into the instrument. The instrument performs the necessary lysis of bacterial cells (if they are present), extracts the nucleic acid, amplifies the target sequence, analyzes the real-time PCR curve, and informs the user of the test results. In addition, Third Wave Technologies (TWT) announced plans to develop a POC test for CYP450 drug metabolizing enzyme genes associated with variations in the metabolism of warfarin.

According to Sec. 493.1256 of CLIA, unless CMS approves an alternate procedure, the laboratory performing this type of testing must perform external quality control (QC) checks at least once per day. QC must test the entire analytical process, and for amplification technologies, include a separate control to check for potential inhibitors of the reaction. To address the requirements, several manufacturers have developed systems that rely on internal controls. For example, the Cepheid GBS system contains several internal controls that monitor the entire analytical process: one to demonstrate that cells are lysed completely, one to demonstrate that reagents are added to the specimen correctly, and a separate internal control to verify the integrity of the amplification process (i.e., to control for potential inhibitors in the sample). Software controls evaluate the amplification curves and assess if results for controls and/or the target sequence in the patient specimen are appropriate. The system also has optical controls loaded on the instrument to verify calibration.

CMS' alternative procedure, Equivalent Quality Control (EQC), allows laboratories to perform external QC procedures once a month or with each new lot of reagent when internal controls adequately control each step in the analytic procedure. However, *amplification methods are excluded from this policy*. As a result, under 493.1256, a laboratory would be required to perform external QC at least once each day, *even when internal controls function more frequently, i.e., with every assay*. In this situation, daily external QC does not add information above that provided by properly designed internal controls for single use, unitized, closed system tests. Daily QC merely increases the indirect cost of performing testing, particularly for conditions, diseases, or variations that are of low testing volume (for example, herpes simplex virus testing). FDA regulations require that the manufacturer submit data to support QC recommendations. While FDA regulations do not prevent a manufacturer from recommending less frequent external QC, FDA regulations are not consistent with the CLIA regulations that regulate clinical laboratories performing this testing. Apparent discrepancies in the regulations and CMS policy with respect to the responsibilities of the laboratory to develop appropriate QC practice (particularly with commercial assays and manufacturers instructions), are leading to wide variations in laboratory practice with respect to QC.

## POSSIBLE SOLUTIONS

The Association for Molecular Pathology (AMP) supports the following solutions:

- Allow CMS to grant waivers of the EQC exclusion for amplification technologies to sponsors that can demonstrate that their internal control systems are appropriate. This could be done in conjunction with FDA review of manufactured kits (where applicable).
- Request that CMS remove the exclusion of amplification technologies from the EQC policy (AMP does not know the mechanism for such a request).
- Directly address QC procedures, including the frequency of external QC in a molecular genetic pathology specialty under CLIA. This forum would be open to public comment. The requirements should be flexible enough to address rapidly evolving technology platforms.
- Develop a standard under CLIA or a standards document through the Clinical Laboratory Standards Institute (CLSI) that would aid manufacturers and laboratories in evaluating whether the internal controls are adequate to support less frequent external QC assessments. CLSI currently is working on two separate documents, one directed towards manufacturers and regulators and another focused on laboratories.

Please contact Wayne W. Grody, MD, PhD, Chair of the AMP Professional Relations Committee at [WGrody@mednet.ucla.edu](mailto:WGrody@mednet.ucla.edu), if we can provide further information.

Sincerely,



Barbara A. Zehnbauer, PhD  
President