

Association for Molecular Pathology

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

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Docket Number 98D-1232: AMP's Response to Guidance for Industry and FDA Staff – Assayed and Unassayed Quality Control Material

AMP is an international not-for-profit educational society representing over 1,400 physicians, doctoral scientists, and medical technologists who perform molecular diagnostic testing based on nucleic acid technology. AMP members practice their specialty in widely diverse settings: 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.

AMP's Mission Statement identifies the Society as “dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics.” Our goal is to represent all members regardless of the setting in which they practice because they are united in the end intent to provide high quality, relevant information for the purpose of directing individual and patient community health management. We acknowledge, however, that different perspectives may emerge from those widely diverse settings. In those instances, our primary responsibility is to comment from the standpoint of molecular testing laboratories and the patients they serve.

Our comments are listed below:

Section III.A - This guidance recommends that the manufacturer assign analyte values at the relevant medical decision points prior to being associated with the assay. This concept is not clear as there are multiple points during laboratory testing where QC material is important: the upper and lower limits of the analytical measurement range, the limit of detection and the clinical reportable range.

We would suggest dividing controls into:

1. Controls for closed type system devices; where every component of the assay, from the sample processing to the result reporting, is supplied by the manufacturer (including instruments, reagents, calibrators, controls etc). QC material for such devices should have assigned value so that lab can monitor accuracy of obtained data.
2. Controls for closed type system devices (such as laboratory developed tests). Values should be assigned to the QC material based on intended use of such material (see below).

Section III.B - The guidance recommends that unassayed quality control material not be assigned any value. Information about target values is important for all QC materials. Only knowing if the value is low, medium, high, abnormal, etc. is ambiguous. Laboratories could potentially not use unassayed QC materials due to lack of information.

Section IV.A - Edit the following to include language highlighted in red. Intended use (including the types of assays and analyzers the material is intended to be used with, **and what specific steps, if not all, of the assay is the QC material intended to monitor**).

Information concerning the composition of the QC material, including:

- Concentrations of each analyte in each level of QC material **and how the values were established (including protocols, reagents, instruments, calibration and QC process)**.
- Analyte source, e.g., human or animal species, synthetic or recombinant. For recombinant nucleic acid material, you should include the vector, the source of the cloned nucleic acid region or gene, and specific nucleic acid sequence. **For amplified nucleic acid, you should indicate the target size or region amplified.** For a microorganism, you should include the strain, and portion of the microorganism, the media or cell line used for culture.
- Safety information, including methods you used to test for infectious agents. When blood products are used, you should include a certification statement that the animal/human source components used in the control are safe and that any blood product derived material has been tested by FDA approved (or equivalently recognized) assays and found to be negative for the communicable disease agents, as stated in 21 CFR Part 610. If inactivation methods have been used for infectious agents, you should describe the methods and the results demonstrating noninfectivity. **You should also demonstrate that such inactivation methods do not influence characteristics of the QC material.**

Section IV.B.1, paragraph 2 – Edit the following to include language highlighted in red. Therefore, we recommend that you evaluate matrix effects of your QC material relative to the intended use human samples and describe relevant findings in the package insert. **This is especially important if “surrogate” QC material is to be used as the matrix may have a different effect on synthetic when compared to natural analyte.**

Section IV.B.1, paragraph 3 – Edit the following to include language highlighted in red. Another related issue is that as a result of differences in matrices, QC materials might differ from patient samples in terms of preparatory steps required for the assay (e.g., dilution, extraction, centrifugation or other pre-treatment). **You should be aware of intra and inter individual variability of patient samples that can affect assay performance (such as the presence of certain drugs, like heparin, or high lipid content in whole blood). Such variability should be either incorporated into the QC material or it should be clearly stated to the end user that the QC material is not designed to control such variability (limitations).**

Section IV.B.2, paragraph 1 – Add the following to the list

- Calibration and quality control that was used in the analyte value assignment

Section V Intended Use- Add the following to the list

- What steps in the assay is the QC material intended to monitor.

See discussion above about assayed or unassayed control material. Given the varied uses of control materials, it is difficult to predict in advance how QC materials will be used in a given assay. Therefore, regardless of the designation of material as assayed versus unassayed, AMP feels it is important that the purchasing laboratory not be constrained in their use of such materials for appropriate qualitative and quantitative purposes. Note in support from the FDA website (www.fda.gov):

“How a QC component is used within a laboratory is not within FDA's jurisdiction. Other Agencies, such as of the Centers for Medicare and Medicaid Services (CMS), the College of American Pathologists (CAP), or the Joint Commission Accrediting Hospital Organization (JCAHO) have jurisdiction over the procedures and practices within laboratories.”

Section V Reagents - Edit the following to include language highlighted in red.

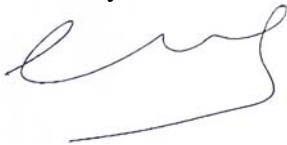
For both assayed and unassayed material you should describe the analyte source (e.g., from human or animal species, synthetic, or purified chemicals). For recombinant nucleic acid material, you should include the vector, the source of the cloned nucleic acid region or gene and specific nucleic acid sequence. **You should also describe how the DNA was extracted.** For a microorganism, you should include the strain, and if applicable, the portion of the microorganism (gene, antigen, etc.). You should describe the media or cell line used for culture.

Section V Assigned target values and ranges

We do not agree that laboratories that the manufacturer used to validate the QC material should be listed on the label. While this may be relevant to the manufacturer's submission package, laboratories may not participate in validation studies if they know that they will be listed on the product label.

Thank you for the opportunity to comment on this very important document. AMP, members are routine users of QC material and want to ensure the highest quality of laboratory testing for molecular pathology. Please do not hesitate to contact V.M. Pratt, PhD, AMP Clinical Practice Committee Chair at victoria.m.pratt@questdiagnostics.com if we can be of further assistance.

Sincerely,



Andrea Ferreira-Gonzalez, PhD
President