AdvaMed – Advanced Medical Technology Association
701 Pennsylvania Avenue, NW, Suite 800
Washington, DC 20004–2654
Tel: 202 783 8700
Fax: 202 783 8750
www.AdvaMedDx.org

EDMA - European Diagnostic Manufacturers Association
Place des Maieurs, 2
1150 Brussels – Belgium
Tel. +32 2 772 2225
Fax +32 2 772 2329
www.edma-ivd.be

October 31, 2011

Dear CLMJE Editors (Drs. Rifai, Plebani, Wu, Brugnara, Delvin, Lamb, Ness, Wick, and Berg):

On behalf of AdvaMed Dx, a Division of the Advanced Medical Technology Association (AdvaMed) and the European Diagnostic Manufacturers Association (EDMA), we submit this letter to the editor in response to the CLMJE editorial and proposed guidelines entitled "Full Disclosure in Industry-Sponsored Laboratory Medicine Research Studies: Statement by the Consortium of Laboratory Medicine Journal Editors" (Rifai N, Plebani M, et al Clin Chem 2011; 57: 359-360).

AdvaMed Dx member companies produce advanced, *in vitro* diagnostic (IVD) tests that facilitate evidence-based medicine, improve quality of patient care, enable early detection of disease and reduce overall health care costs. Functioning as an association within AdvaMed, AdvaMed Dx is the only multi-faceted, policy organization that deals exclusively with issues facing *in vitro* diagnostic companies both in the United States and abroad.

EDMA is the trade association that represents the *in vitro* diagnostic industry active in Europe. EDMA members bring together 22 National Associations in European countries and 43 major companies engaged in the research, development, manufacture or distribution of IVD products. Through its affiliated National Associations, EDMA represents in total more than 500 companies across Europe.

We respectfully request this letter to the editor be published in your journal or alternatively as an opinion letter. If it is necessary and/or you wish to further adapt this letter for publication, please contact us. We are more than happy to work with you or host further discussion. If you have any questions, please do not hesitate to contact us.

Sincerely,

……

Andrew Fish
Executive Director
AdvaMedDx

……

Dr. Volker Oeding
Director General *ad interim*
EDMA

AdvaMed – Advanced Medical Technology Association
701 Pennsylvania Avenue, NW, Suite 800
Washington, DC 20004–2654
Tel: 202 783 8700
Fax: 202 783 8750
www.AdvaMedDx.org

EDMA - European Diagnostic Manufacturers Association
Place des Maieurs, 2
1150 Brussels – Belgium
Tel. +32 2 772 2225
Fax +32 2 772 2329
www.edma-ivd.be

October 31, 2011

Re: Letter to Editor; Proposed Consortium of Laboratory Medicine Journal Editors (CLMJE) Guidelines; Full Disclosure in Industry-Sponsored Laboratory Medicine Research Studies

Dear CLMJE Editors (Drs. Rifai, Plebani, Wu, Brugnara, Delvin, Lamb, Ness, Wick, and Berg):

AdvaMed Dx, a Division of the Advanced Medical Technology Association (AdvaMed), and the European Diagnostic Manufacturers Association (EDMA) submit this letter to the editor in response to the CLMJE editorial and proposed guidelines entitled "Full Disclosure in Industry-Sponsored Laboratory Medicine Research Studies: Statement by the Consortium of Laboratory Medicine Journal Editors" (Rifai N, Plebani M, et al Clin Chem 2011; 57: 359-360).

AdvaMedDx and EDMA strongly support transparency and disclosure of manufacturers' role in clinical research, including identification of the methodology used when diagnostic and prognostic decisions are based on laboratory test results. We agree with the editors that it is important to safeguard the integrity of studies and that all authors should fully disclose potential conflicts of interest. All participants, whether manufacturers or laboratories, should disclose their role, if any, in the design of the study, analysis of the data, and preparation of the manuscript. We are concerned, however, about the potential for unintended consequences that may result with a wide-ranging policy that does not take into account the specific role and objective of certain types of standardization and harmonization studies and the relative state of standardization for a particular analyte. An inflexible policy may be counter-productive and could have a significant and damaging impact on efforts to achieve worldwide harmonization and standardization efforts, and promote use of information that is incomplete and for which it is difficult to interpret specific results where there is inadequate or no harmonization or standardization.

There is a clearly recognized need to continue, and to expand the important efforts that are already underway in the clinical laboratory community to harmonize/standardize methods. It is important to note that harmonization/standardization activities are typically not sponsored by manufacturers, but rather they are sponsored by professional associations/government bodies (e.g., IFCC, NKDEP, NCEP, NGSP). Protocols are designed by the sponsors, not the manufacturers. Industry participates in good faith and supports these efforts as there is no doubt that harmonization/ standardization can lead to improvements in patient care and help ensure that assay results do not present a risk of misinterpretation —including pursuit of early evaluations to understand state of the art, as well as studies intended to define reference methods and reference materials that can be effective in supporting the cause of global harmonization and standardization.

The challenges of achieving standardization are many and often unique to the particular analyte under investigation. It might be useful to emphasize the importance and effectiveness of using "non-linked" data by briefly recounting the successful, longstanding collaboration undertaken by professional groups, standards providers, proficiency providers, and IVD manufacturers to achieve standardization of serum cholesterol measurements. With the Centers for Disease Control and Prevention (CDC) taking the lead in the development of reference methods, along with full cooperation of most of the major suppliers of commercial cholesterol assays, success was achieved only after

1. The variability among methods was shown to be unacceptable, but only when patient specimens were used to compare methods—overall variability included contributions both from the commercial assays as well as from the standardization laboratories' which used a candidate reference method;

2. External proficiency materials from various well-established proficiency providers were demonstrated to not be representative of commercial method performance with patient specimens (i.e., they were not commutable with patient samples); and

3. The candidate reference method (initial GC mass spec protocol) was shown to include a bias of almost 2%, a very large portion of the desired accuracy target (+/-3%).

This example is illustrative of our concerns because the entire laboratory medicine community, including IVD manufacturers, was focused on accurate measurements of patient samples, but it was not possible to assess "truth" with available benchmarks (i.e., proficiency materials) until appropriate specimens for analysis could be defined and the reference method could be improved to provide a definitive, well controlled procedure (among the participating reference laboratories, also participating anonymously) that was free of bias, supporting reliable assessments of the commercial methods. As the accuracy requirements for cholesterol were tightened, even a small error in the reference method could have had significant consequences in the confidence of patient results and on the development costs associated with improving the routine methods of analysis. We firmly believe that such progress would not have been made without the highly cooperative nature of the interactions among all parties, which included anonymity of results from both manufacturers and reference laboratories, while multiple factors and converging variables were still in play and not yet fully understood.

This example also highlights inherent and significant differences with device and drug development. In contrast to therapeutics, device technologies evolve in an iterative progression with continual, incremental improvements over time. Given the number and variety of diagnostic tests and their varying purposes, assessment must be drawn carefully. As mentioned, absence of a gold standard can make it difficult to develop clinical truth. These considerations reinforce the need to recognize these relevant issues in assessment and worldwide standardization and harmonization efforts.

Furthermore, the editorial itself references International Committee of Medical Journal Editors (ICMJE) policies regarding investigator participation in a designated registry and disclosure of conflicts of interest. We fully support compliance with such policies, and note that the Food and Drug Administration Amendments Act of 2007 (FDAAA) provided for delayed disclosure of device clinical trial registry information until at least the date of clearance or approval. Such provision was intended to support ongoing medical device innovation for patient care, particularly of small device companies, by ensuring that sensitive, confidential commercial information is protected from public disclosure until after FDA approval or clearance. Such disclosure could have the unintended consequence of eliminating many small device innovators from the market place, including orphan markets. A number of comparison and harmonization studies include premarket and early stage research data, which raises special concerns regarding disclosure of such

laboratory test methods and manufacturers.

Additionally, we believe it is incorrect to assume that an appropriate mitigation is possible such as "[i]f authors sincerely believe that the scientific findings would be incorrectly interpreted based on such disclosure, they should articulate the appropriate use and limitations of the information in the text of the manuscript". Inclusion of information and/or warnings regarding inappropriate uses of study data in the "Limitations" section of a journal article simply does not achieve the visibility of the Results or Conclusions sections, and thus would not achieve the intent.
We believe that an inflexible stance in which "results must always be tied to specific methods" in publications of harmonization/ standardization studies would have the following unintended consequences:

- Manufacturers may not agree to participate in these studies when their results could be misinterpreted in a manner that might cast doubt on aspects of their assay's performance;

- Manufacturers may not agree to include products that are still under development in these studies for fear of disclosure of sensitive, confidential commercial information;

- Manufacturers may choose not to include their methods in early stage studies when the risk of misinterpretations of results from commercial methods is likely to be greatest; and

- Smaller manufacturers may not choose to participate at all since risks would be perceived as intolerable due to their smaller portfolio of products.

We also request the editors consider that initiating such an immediate change for publication without prior notice might put authors at risk of conflict with prior agreements for studies currently in progress.

Journal editors should consider each study in light of the state of the harmonization/ standardization of the analyte in question. For example, recognized standards (methods and materials) may not exist for the analyte and early lifecycle studies may need to be performed to survey whether there is need for improved standardization, and/or determine how large the gap may be in state of the art. The study may include data regarding an early stage research assay that has not yet received regulatory approval. Furthermore, a reference method, or commutable primary or secondary reference preparations may not be available for manufacturers to use. Depending on the analyte being examined, the harmonization/standardization activities may take years, often due to difficulty in finding a reference material that is commutable among various methods. During this time, there may be occasional updates from the working group in which they demonstrate progress that has been made, although harmonization/standardization has not yet been achieved.

We support disclosure in later stage harmonization and standardization studies, but judgments with regard to the quality of assays should be rendered only with the utmost care taking into account the study design. Samples chosen for use in comparative standardization studies do not necessarily represent samples typically used for routine method comparisons, nor are they necessarily representative of typical patient samples encountered in most routine laboratory analyses. Study sponsors will at times choose samples that are known to be problematic, to emphasize generic methodological issues, not specific to any single commercial method. When appropriate specimens from similar or identical patient populations are used in comparison studies in which the methods are used according to manufacturers' instructions or in accord with published literature, reported results should be associated with the methods from which they were derived.

Furthermore, we ask the members of CLMJE to consider more flexibility in the timeline for implementation of this policy to consider our comments and allow an appropriate transition time for impacted studies. This is particularly important with such a new policy in order to honor any pre-existing agreements between the study sponsors and manufacturers for studies already in progress prior to publication of this policy. And finally, the CLMJE editors should have flexibility to consider the purpose of cooperative published studies, such as those used for standardization and harmonization, to determine if linking results to the methods included in the study (both routine commercial methods and those developed and offered by clinical laboratories) add value and information that will help achieve better patient care.

Thank you for your consideration of this important issue.

Respectfully,

…… ……

Andrew Fish
Executive Director
AdvaMedDx

Dr. Volker Oeding
Director General *ad interim*
EDMA