Harmonization of Liquid Chromatography–Tandem Mass Spectrometry Protein Assays

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KEYWORDS

• LC-MS/MS • Protein • Harmonization • Standardization

KEY POINTS

- Rigorous approaches to harmonization and standardization of clinical assays have been published.
- Less-formal approaches to standardization can serve a useful purpose of improving harmonization of liquid chromatography–tandem mass spectrometry (LC-MS/MS) assays before the completion of formal harmonization projects.
- Factors that can affect the harmonization process are discussed with particular emphasis on LC-MS/MS protein assays.

INTRODUCTION

Harmonization of diagnostic test results is fundamental to the effective use of laboratory testing in the diagnosis, treatment, and monitoring of disease. Working in an environment without any effort for diagnostic test harmonization might lead to diagnostic and therapeutic mistakes.

The International Consortium for Harmonization of Clinical Laboratory Results, convened in 2010, published a position statement[1] that defined 2 concepts; standardization ("uniformity of test results based on relation to a reference method") and harmonization ("uniformity of test results when a reference method is not available"). Although this statement is recent, it recognizes and elevates an old problem in

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laboratory medicine, the need for laboratory measurements to be equivalent within agreed and meaningful limits.

Several laboratory tests that have population-wide impact on human health have undergone this process (eg, cholesterol, glucose, hemoglobin A1c); however, few if any mass spectrometry–based methods have reached a level of harmonization or standardization presented in the American Association for Clinical Chemistry (AACC) position statement. In this respect, mass spectrometry (MS) is not unique because relatively few tests in the clinical laboratory have undergone the rigorous harmonization process advocated in this document. The present article discusses some of the issues relevant to MS-based assay harmonization and standardization with a focus on proteins.

APPROACHES TO HARMONIZATION AND STANDARDIZATION

Harmonization and standardization is a formal effort among a wide range of stakeholders that start with the definition of a clinically relevant measurand. Subsequently, measurement methods are obtained (or developed) and evaluated for their ability to reproducibly determine the measurand in patient samples. For methods that will ultimately be standardized, reference methods and materials are developed in parallel so that traceability can ultimately be achieved. A roadmap for this process has been described.[2] Key components of this approach are illustrated in **Figs. 1** and **2**.

Standardization takes the concept of harmonization to a higher level: methods are not just harmonized with each other, but also with an agreed-on absolute standard of

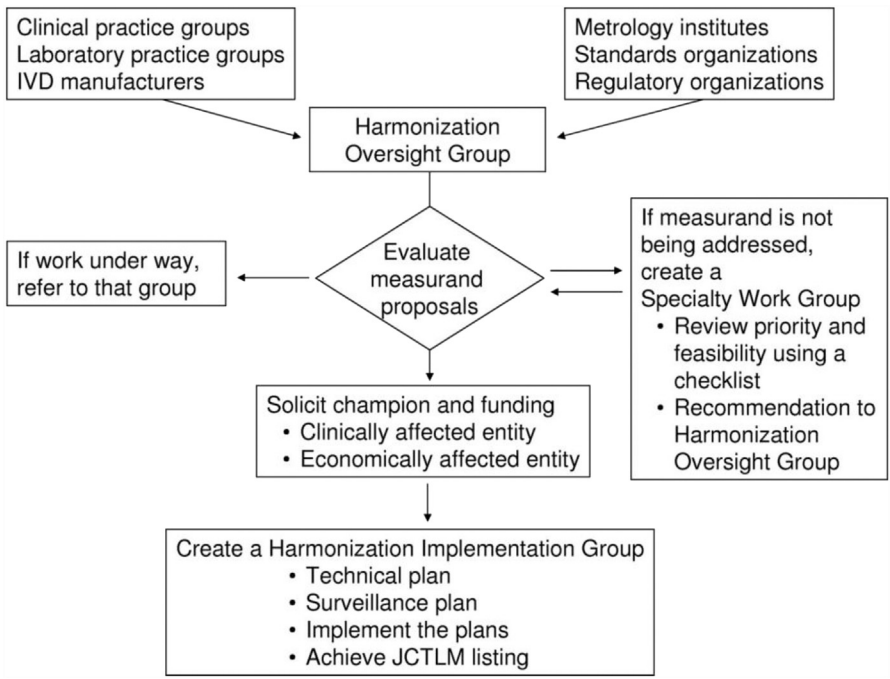

Fig. 1. Overview of a general approach to manage harmonization of a measurand. IVD, in vitro diagnostic; JCTLM, Joint Committee for Traceability of Laboratory Medicine. Greg Miller W, Myers GL, Lou Gantzer M, et al. Roadmap for Harmonization of Clinical Laboratory Measurement Procedures Clinical Chemistry 2011;57(8):1108–17; *Reproduced with permission from* the American Association for Clinical Chemistry.