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A "Step-Up" approach for harmonization

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ABSTRACT

According to the measurement paradigm, assays claiming the same measurand should give equivalent results within clinically relevant constraints. The key to accomplish this paradigm is standardization of assays to an SI-traceable reference measurement system. However, measurement results for complex analytes often are not expressed in SI-, but in arbitrary units, defined, for example, by an international conventional measurement standard. Traceability to such a standard mostly does not lead to among assay equivalence. To achieve this, the concept of harmonization has been proposed. We describe here the practical aspects involved with the "Step-Up" design. It essentially comprises a sequence of method comparisons with selected sets of commutable samples. The outcome of each phase allows to decide whether the step-up to the next phase can be set. The harmonization process itself uses a statistically valid location measure as surrogate reference measurement procedure. The design also foresees a protocol for sustaining the first-established harmonization status. For the design to be successful, it is essential that as many assays as possible are involved in the method comparison leading to the harmonization target, and that it can be shown that they sufficiently correlate to that target with consistency of performance over the covered measurement range.

1. Introduction

According to the measurement paradigm, routine measurement procedures (further also referred to as assays) claiming the same measurand should give comparable results within clinically relevant constraints. It is generally accepted that for compliance with this paradigm, a reference measurement system is required to establish metrological traceability to a reference, which can be the definition of a measurement unit, a measurement procedure or a measurement standard [1]. A reference measurement system comprises different levels of materials and measurement procedures, and is intended for use as an unbroken calibration hierarchy. In the ideal scenario, the reference and hence the highest level of the reference measurement system is the Système International d'Unités (SI) and its embodiment/materialization in a primary calibrator. By establishment of metrological traceability to the SI, hierarchically lower assays are enabled to express measurement results in terms of the values obtained at the highest available level. In other words, the measurement paradigm is accomplished within the constraints of measurement uncertainty. The process of establishing SI-traceability is also called standardization, and is described in the ISO 17511 [1,2]. However, for a multitude of measurands, the SI does not yet apply, in particular when the components in the measurand comprise a (micro)heterogeneous mixture. In this case measurement results are expressed in arbitrary units, for example, International Units (IUs) as defined by an international conventional measurement standard from the World Health Organization (WHO). The level at which metrological traceability stops for these measurands depends on the availability of higher order measurement procedures and calibrators. In this regard, the ISO 17511 distinguishes different categories of metrological traceability [2]. In contrast to traceability to the SI, traceability to an international conventional measurement standard does not necessarily lead to compliance with the measurement paradigm. Non-commutability of the measurement standard may be a major reason [2]. Notwithstanding this, also for measurements traceable to another reference than the SI, harmonization is considered highly desirable [3]. Recently, 2 major steps have been set in this direction. The first one consisted in the proposal of a harmonization approach for protein measurements [4], while the second one aims at establishing an overarching control system of the harmonization process in all its aspects [5].

Here we will deal with the practical aspects involved with the harmonization approach described in theory earlier [4]. It starts with the definition of the measurand, commensurate with its realization by a measurement standard. The latter should be a panel of commutable clinical samples from single donations. It should be used in a method comparison study with the assays examined for harmonization, whereby the samples should be assigned with a statistically valid target (= surrogate reference measurement procedure). This can be the trimmed mean, weighted mean, median or another statistical locator.

Abbreviations: SI, Système International d'Unités; IUs, International Units; WHO, World Health Organization; IFCC, International Federation of Clinical Chemistry and laboratory Medicine; APTM, All-procedure trimmed mean.

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Statistical methods to estimate a harmonization target have been elaborated before, e.g., principal component analysis, and were recently challenged by a proof of concept study [6–9]. For the approach to be successful, it is essential that as many assays/manufacturers as possible are involved in the method comparison leading to the harmonization target, that the assays' performance is shown to be consistent over the covered measurement interval (concentrations typically found in the intended diagnostic application of the assay), and that the assays have a certain degree of maturity for the in-vitro diagnostic measurement of the heterogeneous analyte. This requires, for example, demonstration of sufficient correlation of individual assays to the mean, and performance with sufficient accuracy. The latter should be estimated from the deviation of the results for individual samples from the sample mean. As long as the measurement of a heterogeneous analyte has not reached this degree of maturity, it may be better to postpone harmonization, because the requirements for success are missing.

In view of the fact that obtaining clinical relevant samples of good quality, in sufficient volume and sourced within an acceptable time frame, may be extremely challenging, we propose to gradually proceed with the method comparison in terms of samples used [10]. One should start with easily to source samples from apparently healthy volunteers, so that familiarization with the process is possible and evidence for successful harmonization is built. Therefore, we propose a "Step-Up" design. As suggested by the name, it comprises a sequence of phases to enable the decision that it is appropriate to step-up to the next phase.

For evidence of the feasibility of the "Step-Up" approach, we refer to an ongoing project from the International Federation of Clinical Chemistry and laboratory Medicine (IFCC) for harmonization of thyrotropin (TSH) measurements [11–13]. Meanwhile this project has successfully conducted several method comparison studies and developed a statistical procedure for deriving a harmonization target (personal communication; report in preparation for publication).

2. The "Step-Up" Design for Harmonization

The "Step-Up" design is schematically represented in Fig. 1, while Fig. 2 summarizes the sub processes of each phase, as described below.

2.1. "Familiarization phase" (Phase 1)

2.1.1. Objectives

The "Familiarization phase" (i) provides a general picture of the intrinsic quality and comparability of assays by use of high-volume single donation samples from apparently healthy volunteers (note: the intrinsic quality of an assay is reflected by performance attributes such as imprecision, within-run stability, between-run differences, calibration consistency, etc.); (ii) allows a decision to step-up to phase 2 that uses lower-volume samples (both from apparently healthy and diseased volunteers).

As a surplus, phase 1 should reveal unforeseen obstacles to overcome before setting the step to the use of precious and difficult to source clinical samples. Moreover, it gives all participants the opportunity to grow in the project by getting familiar with the used process.

2.1.2. Donor selection and sample production

Investigation of the performance attributes requires a method comparison with use of high-volume single donation samples. As explained before, such samples are best to obtain from apparently healthy volunteers.

To put together a suitable panel it is recommended to select 40 samples out of a pool of maybe 200 by screening for the target analyte. This gives the opportunity to cover a reasonable interval of (so-called) 'normal' concentrations. It is also crucial to use a validated protocol for sample production resulting in unadulterated single donor serum samples, e.g., based on the C37-A protocol, but without pooling/filtration

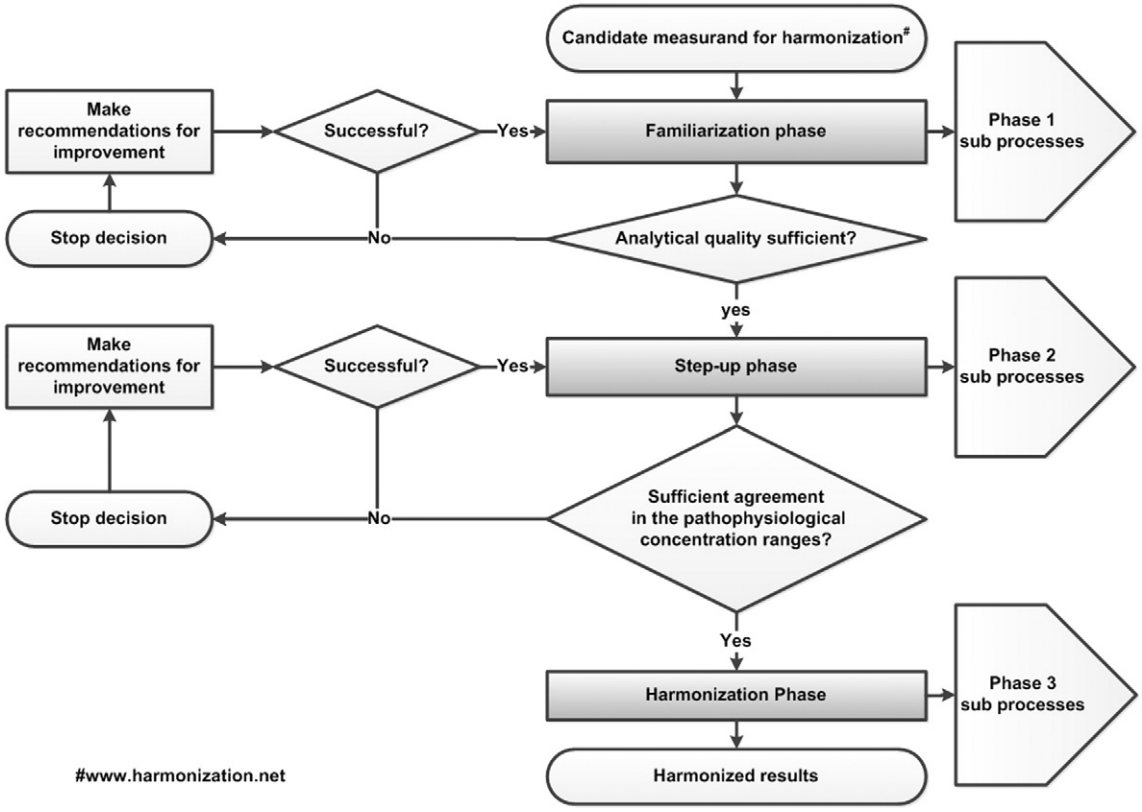

Fig. 1. Flow chart of the "Step-Up" design.