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Verification of in vitro medical diagnostics (IVD) metrological traceability: Responsibilities and strategies

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ABSTRACT

To be accurate and equivalent, laboratory results should be traceable to higher-order references. Furthermore, their analytical performance should fulfill acceptable measurement uncertainty criteria defined to fit the intended clinical use. With this aim, In Vitro Diagnostics (IVD) manufacturers should define a calibration hierarchy to assign traceable values to their system calibrators and to fulfill during this process uncertainty limits for calibrators, which should represent a proportion of the uncertainty budget allowed for laboratory results. It is important that end-users may know and verify how manufacturers have implemented the traceability of their calibrators and estimated the corresponding uncertainty. However, full information about traceability and combined uncertainty of calibrators is currently not available. Important tools for IVD traceability surveillance are the verification by laboratories of the consistency of declared performance during daily operations performed in accordance with the manufacturer's instructions and the organization of appropriately structured External Quality Assessment (EQA) programs. The former activity should be accomplished by analyzing system control materials and confirming that current measurements are in the manufacturer's established control range. With regard to EQA, it is mandatory that target values for materials are assigned with reference procedures by accredited laboratories, that materials are commutable and that a clinically allowable inaccuracy for participant's results is defined.

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1. Introduction ("Plan")

The main objective of Laboratory Medicine is to provide useful information for the formulation of correct clinical decision-making in order to significantly contribute to the quality of health-care. Focusing on analytical aspects of clinical laboratory measurements, such an objective can only be achieved through the production of accurate and equivalent results, regardless of laboratory and/or analytical system used to produce them [1]. There is now an international consensus that to achieve this goal it is essential to define and enforce, for each measured analyte, a reference measurement system based on the implementation of metrological traceability of patients' results to higher-order references (materials and methods) together with a clinically acceptable level of measurement uncertainty [2]. In particular, it is

essential to build an unbroken metrological traceability chain, whereby In Vitro Diagnostics (IVD)¹ manufacturers can implement a reliable transfer of the measurement trueness from the highest level of the metrological hierarchy to calibrators of commercial methods used in clinical laboratories. The European Union (EU) Directive 98/78 on IVD medical devices [3], supported by two specific ISO standards [4,5], requires manufacturers to ensure traceability of their analytical systems to recognized higher-order references. Compliance with the IVD Directive is indicated

¹ Nonstandard abbreviations: IVD, In Vitro Diagnostics; EU, European Union; CE, Communautés Européennes; JCTLM, Joint Committee for Traceability in Laboratory Medicine; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; u_c , combined standard uncertainty; C-RIDL, Committee on Reference Intervals and Decision Limits; WG-AETR, Working Group on Allowable Error for Traceable Results; TEa, total allowable error; IUPAC, International Union of Pure and Applied Chemistry; OG_U , optimal goal of expanded uncertainty; DG_U , desirable goal of expanded uncertainty; MG_U , minimum goal of expanded uncertainty; CV_i , intraindividual biological coefficient of variation; u , standard uncertainty; SIBioC, Italian Society of Clinical Biochemistry and Clinical Molecular Biology – Laboratory Medicine; SI, International System of measurement; NIST, National Institute for Standards and Technology; GC-IDMS, isotope dilution-mass spectrometry coupled to gas chromatography; CDC, Centers for Disease Control; EQA, External Quality Assessment; RELA, Reference Laboratories.

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through the CE (“Communautés Européennes”) marking of conformity on diagnostic products, but at present no normative validation or verification by a third party of the manufacturer’s statements and certifications is provided [6].

The Joint Committee for Traceability in Laboratory Medicine (JCTLM) is an international committee created in 2002 by the Bureau International des Poids et Mesures, International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and International Laboratory Accreditation Cooperation, with the task of defining, on the basis of an evaluation process with objective quality criteria, a database containing lists of the three pillars of metrological traceability and standardization, viz. a) higher-order reference materials, b) higher-order reference methods and c) accredited reference laboratory services [7]. This information is offered to IVD manufacturers to assist them in following the EU Directive on compliance and traceability of commercial systems. Moreover, JCTLM should make available, in addition to already existing lists of the three main components of metrological chains, metrological reference measurement systems for each analyte in their entirety, including the estimation of associated average combined standard uncertainty (u_c) values at various levels of the metrological chain [8,9]. In addition to the JCTLM database describing information on the three main pillars (reference methods and materials and accredited reference laboratories) needed to implement standardization in clinical practice, in 2005 the IFCC through the creation of the Committee on Reference Intervals and Decision Limits (C-RIDL) started to describe a fourth pillar represented by traceable reference intervals [10,11]. In fact, reference intervals obtained with analytical systems that produce results traceable to the corresponding reference system can be transferred among laboratories, provided that the served populations have the same biological characteristics, so helping to eliminate the confusion caused by different reference intervals employed for the same analyte. More recently, an appropriately organized analytical (internal and external) quality control program has been described as the fifth pillar of laboratory standardization [8].

An aspect not yet completely considered, substantially distinguishing the application of metrological science in Laboratory Medicine from that in other areas, is that the definition and use of the reference system concept for standardization of measurements must be closely associated with the setting of targets for uncertainty and error of measurement in order to make it clinically acceptable [2,8]. If these goals are not

objectively defined and fulfilled, there is a risk of letting error gain the upper hand, thus obscuring the clinical information supplied by the result and possibly nullifying the theoretical advantages of metrological traceability and even causing negative effects on patients’ outcome. Therefore, they represent the sixth pillar sustaining the “temple” of laboratory standardization (Fig. 1). With regard to this point, we recently highlighted the importance of a selected traceability chain for the definition of analytical goals [9,12].

In agreement with recommendations by the IFCC Working Group on Allowable Error for Traceable Results (WG-AETR), two limits must be defined for an adequate clinical application of laboratory measurements once a traceability chain has been defined, viz. a) the allowable limit for the expanded u_c of manufacturer’s commercial calibrators and b) the total allowable error (TEa) for measurements done by individual clinical laboratories [13]. An important part of the debate focuses on how these limits should be defined. In 1999, the IFCC-International Union of Pure and Applied Chemistry (IUPAC) conference held in Stockholm established the hierarchy of sources for deriving the analytical goals of a laboratory measurement [14]. Although the most reliable approach consists in establishing the allowable limits after performing experimental studies evaluating the clinical impact of measurements, unfortunately such studies are difficult to carry out resulting in limited data on few analytes [15,16]. It is therefore accepted that, in the absence of data on clinical outcome, one may derive the information from biological variability components of the analyte [17]. In agreement with this approach, the acceptable limit for expanded u_c associated with commercial calibrators should correspond to a fraction (e.g. 50%) of the goal [optimal (OG_U), desirable (DG_U) or minimal (MG_U), depending on the average performance provided by available commercial assays] of imprecision (calculated as $OG_U \leq 0.25 CV_I$, $DG_U \leq 0.50 CV_I$ or $MG_U \leq 0.75 CV_I$, where CV_I is the average value of intraindividual biological CV for the considered analyte). In agreement with the metrological traceability theory, the systematic error (bias) of the calibrator must be corrected if present in a non-negligible amount [18]. Recently, Stepman et al. [19] questioned the use of targets other than OG_U as this already results in a 30% increase of false clinical decisions. The TEa limit for measurements performed by individual laboratories can also be derived from biological variability data of the analyte using the classical approach described by Fraser et al. [17], with goals suitably modulated on three quality levels (minimal, desirable or optimal) [13].

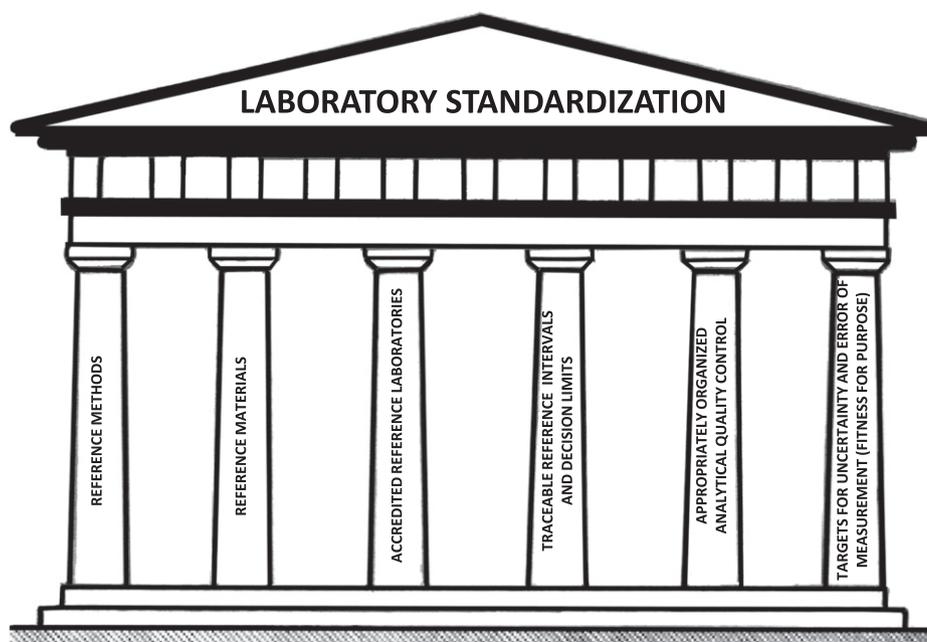


Fig. 1. The temple of laboratory standardization and its six pillars.

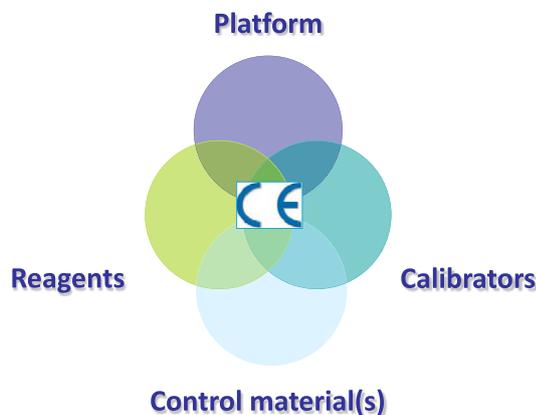


Fig. 2. Components of the analytical system (instrument, reagents, calibrators and materials for system alignment verification) that only as such (as a whole) is certified (“CE marked”) by the manufacturer in terms of traceability to the reference measurement system.

2. The role of diagnostic manufacturers (“Do”)

As mentioned above, diagnostic manufacturers are required by the EU Directive to ensure the metrological traceability of their analytical systems to the available higher-order references [6]. If the manufacturer assumes total responsibility for supplying products of acceptable quality in terms of traceability and uncertainty of the system (“CE marked”), it is no longer possible to consider separately the components of each analytical system (i.e., platform, reagents, calibrators and control materials), which in terms of performance can only be guaranteed and certified by the manufacturer as a whole (Fig. 2). Any change introduced by users or third parties (for instance, the use of reagents, calibrators or control materials from other suppliers) may significantly alter the quality of the analytical system performance, removing any responsibility from the manufacturer and depriving the system (and, consequently, the produced results) of the certification originally provided through CE marking. On the other hand, a paradigm shift in the thinking of IVD manufacturers themselves is needed that should place alongside the traditional strategy of commercial competition with the production of accurate and equivalent results.

We must emphasize that traceability implementation by manufacturers is necessary but not sufficient to achieve an effective use of diagnostic systems by clinical laboratories. Indeed, it must be associated with the demonstration that the commercial system meets the analytical goals established for its clinical use. In this regard, the manufacturer must indicate (upon user's request) the u_c associated with calibrators when used in conjunction with other components of the analytical system (platform and reagents) [2]. It is important to point out that such uncertainty estimates provided by manufacturers should be the u_c , including the uncertainty associated with higher levels of the metrological traceability chain [8,9,20]. Only in this way can the provided information be used by both manufacturer and user to compare with the maximal acceptable u_c limit defined for that measurement [13]. It is very important to stress this aspect because the uncertainty value of calibrators usually declared by manufacturers is only that related to their standard uncertainty (u). For instance, during a study for evaluating the accuracy of serum albumin measurement with the Tina-quant Albumin Gen. 2-Cobas c501 system (Roche Diagnostics) [21], we were surprised to see that the uncertainty declared by the company for its commercial calibrator (C.f.a.s. PUC), of 1.31%, was lower than that declared for the reference material ERM-DA470 (2.01%) used by the same company to transfer the measurement trueness [22]. Knowing the protocol applied by Roche for deriving the uncertainty value of calibrators and being consequently able to exclude errors in its experimental estimate [23], it is

evident that the value stated in the calibrator traceability and uncertainty document merely corresponded to its u , without including the uncertainty of the previous steps of traceability chain. For a proper evaluation of analytical performance and associated uncertainty of the commercial system, these earlier steps cannot be ignored [8]. A recommendation about the type of uncertainty that must be provided by manufacturers at the calibrator level, in addition to the need to standardize the approach employed by manufacturers to estimate it, is therefore urgent.

Using serum albumin measurement as an example makes clearer the issues just discussed. The reference measurement system for this protein has clearly been described [8,24,25]. Therefore, in this specific case, the role of IVD manufacturers is to implement an internal calibration hierarchy from currently available secondary reference material (ERM-DA470k/IFCC provided by the EU Institute for Reference Materials and Measurements) to transfer the measurement trueness to commercial calibrators. In this way, they will ultimately be traceable to the U.S. National Reference Preparation no. 12-0575C, the highest reference of albumin metrological chain [24]. It was previously emphasized that to perform this work of trueness transfer in an effective way the employed reference material must be commutable [26]. In this regard, the ERM-DA470k/IFCC has in measuring albumin the same behavior as native human sera (i.e. it is commutable) and can, therefore, be used to ensure the traceability of commercial assays to the reference measurement system [27]. The problem is, however, that the expanded u_c of 3.22% associated with this material is already greater than the total uncertainty budget for serum albumin measurement as derived from biological variability of the analyte ($MG_U \leq 2.33\%$) [8,25]. Moreover, the imprecision of available commercial methods usually fails to meet the high quality requirement, further worsening the situation [28]. The expanded u_c associated with the serum albumin results on patient specimens [basically including the u_c of corresponding traceability chain, multiplied by the coverage factor of 2 (95% level of confidence) and the uncertainty due to “random effects” in the laboratory (i.e., the imprecision of the measurement)] is, therefore, on average at least 2 times greater than MG_U , showing that the uncertainty of albumin measurement in serum is probably too high to meet the requirements of analytical quality established for its clinical application [25]. The albumin case, similar to that of glycated hemoglobin [9], is a good example of an analyte for which it should be a priority to significantly reduce the uncertainty associated at the upper levels of the metrological chain as well as to improve the performance of commercial methods. Similar examples related to other analytes are available in the WG-AETR document [13].

3. The role of the profession (“Check”)

Once the reference measurement system and associated clinically acceptable analytical goals have been defined and IVD manufacturers have designed commercial systems (including platform, reagents, calibrators and control materials) that meet the requirements of traceability and established quality, it is the task of end-users, i.e. clinical laboratory profession, to verify that the alignment process has been correctly implemented and that the performance of marketed systems is appropriate for their clinical use [2].

3.1. Availability and quality of information

To our knowledge, there are no studies carried out to specifically evaluate how much information regarding metrological traceability of IVD systems is obtainable from manufacturers. It is quite a common experience to note that inserts of calibrators and reagents give a very partial, sometimes confusing picture. More complete information is usually obtainable by directly contacting the manufacturers but not without difficulty and delay.

In principle, laboratory users should be able to access the following: a) an indication of higher-order references (materials and/or procedures) used to assign traceable values to calibrators, b) which internal

Table 1
Metrological traceability and uncertainty information derived from calibrator package inserts of commercial systems measuring blood glucose marketed by four IVD companies.

Company	Platform	Principle of commercial method	Calibrator	Declared standard uncertainty ^a	Higher-order reference employed		Type of traceability chain used ^b	Combined standard uncertainty associated with the used chain ^c
					Method	Material		
Abbott	Architect	ND	Multiconstituent calibrator	2.70%	IDMS	NIST SRM 965	A	1.22–1.45% ^d
Beckman	AU	Hexokinase	System calibrator	ND	ND	NIST SRM 965	A	1.22–1.45% ^d
	Synchron	Hexokinase	Synchron multicalibrator	ND	ND	NIST SRM 917a	D	1.60–3.00% ^e
Roche	Cobas c	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
	Integra	Hexokinase	C.f.a.s.	0.62%	IDMS	ND	B	1.70%
	Modular	Hexokinase	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
		GOD	C.f.a.s.	0.84%	IDMS	ND	B	1.70%
Siemens	Advia	Hexokinase	Chemistry calibrator	1.30%	Hexokinase	NIST SRM 917a	C	1.88–3.26% ^f
		GOD	Chemistry calibrator	0.80%	Hexokinase	NIST SRM 917a	C	1.88–3.26% ^f

ND, not declared; IDMS, isotopic dilution-mass spectrometry; NIST, National Institute of Standards and Technology; SRM, standard reference material; GOD, glucose-oxidase method.

^a Expanded with a coverage factor of 2 (except for Siemens, undeclared).

^b See Fig. 3 for more information.

^c Expanded with a coverage factor of 2.

^d Uncertainty depends on the concentration level of NIST SRM 965 [29].

^e Uncertainty depends on the concentration level of calibration curve prepared with NIST SRM 917 [13].

^f Uncertainty depends on the concentration level of biological samples used for correlation (CIRME data, from ref. [30]).

calibration hierarchy has been applied by the manufacturer and, in this case, c) a detailed description of each step, d) the u_c value of commercial calibrators, and e) which, if any, acceptable limits for uncertainty of calibrators were applied in the validation of the analytical system. All this information should be available in the assay or calibrator package inserts, clearly indicating the connection between the two [e.g. “the expanded u_c associated with the calibrator X when used in the analytical system Y (analyzer A with reagent B) for the measurement of the analyte Z is equal to 1.3%”].

Recently, the Working Group on Analytical Quality of the Italian Society of Clinical Biochemistry and Clinical Molecular Biology – Laboratory Medicine (SIBioC) carried out a preliminary investigation regarding the availability of this information. They consulted commercial calibrator package inserts and on-line associated information of four major IVD companies (Abbott Diagnostics, Beckman Coulter, Roche Diagnostics

and Siemens Healthcare Diagnostics) used in the measurement of some common analytes in serum or plasma for which a metrological reference system is available. Table 1 shows results obtained for plasma glucose measurement.

With regard to metrological aspects, manufacturers only declare the name of the reference material and/or method to which the system calibration is traceable, without any indication regarding the internal procedure followed for the application of the selected metrological traceability chain. In the case of glucose, to assign values to commercial calibrators that are traceable to the International System (SI) of measurement it is possible to use at least four different types of metrological traceability chain (Fig. 3).

The first option, the most current one and possibly associated with less accumulation of uncertainty during various trueness transfer steps, consists of use by the IVD company of the secondary reference material

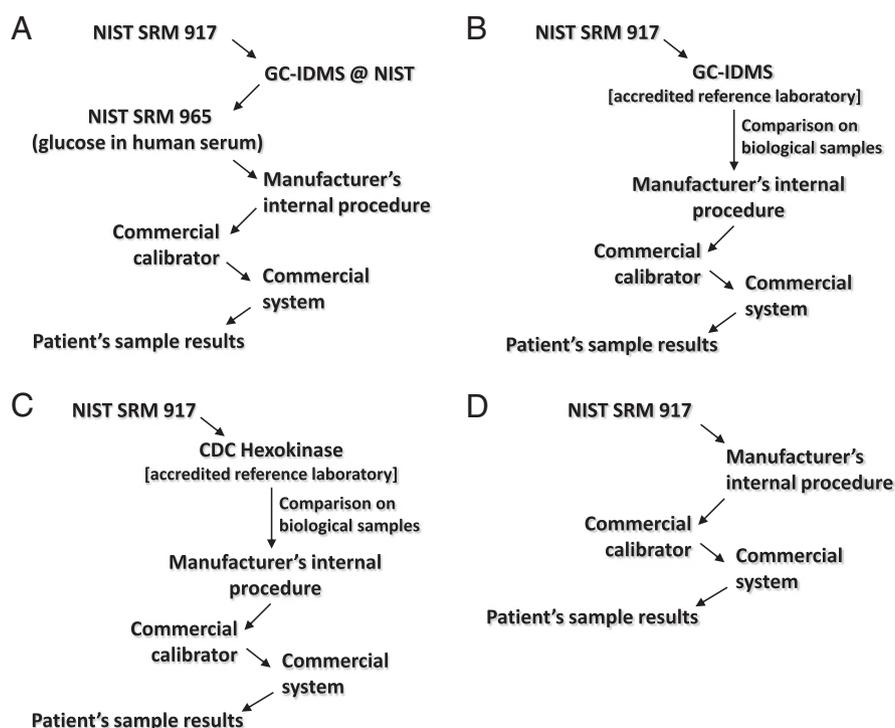


Fig. 3. Types of metrological chains that can be used to implement the traceability of blood glucose results. NIST, National Institute of Standards and Technology; SRM, standard reference material; GC-IDMS, isotope dilution-mass spectrometry coupled to gas chromatography; CDC, Centers for Disease Control.

SRM 965 (glucose in frozen human serum), provided by the National Institute for Standards and Technology (NIST) at four concentration levels, whose values have been assigned at NIST by the reference procedure based on isotope dilution-mass spectrometry coupled to gas chromatography (GC-IDMS) calibrated in turn with the NIST SRM 917 primary reference material (D-glucose powder, purity ~99.7%) with an expanded u_c between 1.22% and 1.45% (Fig. 3A) [29]. By using SRM 965 to directly calibrate the selected internal procedure, the manufacturer can quite easily implement an internal calibration hierarchy for value assignment to the commercial calibrator. For plasma glucose measurements on patient samples the acceptable limits derived from its CV_I are 3.1% (DG_U) and 4.6% (MG_U), respectively [13]. Using this approach to implement traceability, there is still more than 50% of the uncertainty budget with the DG_U limit and more than 70% with the MG_U for the next internal steps of trueness transfer made by the manufacturer and for the imprecision of the measurements performed in the laboratory using the corresponding commercial analytical system.

A second type of metrological chain for glucose measurement provides, as an alternative to SRM 965, the use as secondary calibrator of a panel of biological samples, commutable by definition, whose values (and associated uncertainty) are assigned by the GC-IDMS reference procedure during a comparison experiment between an accredited reference laboratory performing it and the manufacturer's internal procedure (Fig. 3B). The possibility to correct the experimentally estimated systematic bias, if any, ensures the alignment of the manufacturer's internal procedure to the higher-order references, allowing its use for the assignment of traceable values to the commercial calibrator. This approach is associated with an expanded u_c of the secondary calibrator (i.e. the sample panel) slightly higher than that given above, but usually not exceeding the value of 1.70% [30], corresponding to less than 40% of the total uncertainty budget if MG_U is applied.

The metrological chain shown in Fig. 3C is based on the same approach as the previous one, with the difference that the employed reference procedure is the spectrophotometry method originally proposed by the U.S. Centers for Disease Control (CDC), based on the enzymic reaction catalyzed by hexokinase. Given the greater uncertainty associated with this procedure when compared with GC-IDMS, this approach generally shows significantly higher values of uncertainty. In the experience of our reference center, depending on the glucose concentration in analyzed samples, expanded u_c can vary from 1.80% to 3.30% [30], making it more difficult to achieve the acceptable limits of measurement uncertainty in a clinical setting.

The last option that can be used to assign traceable values to commercial calibrators is the one shown in Fig. 3D. In this case, the manufacturer directly uses NIST SRM 917, a powder of highly pure D-glucose, and prepares by gravimetry (that therefore works as the reference procedure) aqueous calibrators of different concentrations, used for the construction of a calibration curve for the manufacturer's internal procedure. The expanded u_c associated with the set of calibrators prepared with SRM 917 (from 1.6% to 3.0%) is such as to make difficult the achievement of acceptable uncertainty limits [13]. In addition, the commutability of aqueous solutions derived from SRM 917 should not be taken for granted and must be experimentally demonstrated.

On the basis of information obtained from companies, displayed in Table 1, the approach described in Fig. 3 as type A chain seems to be used by Abbott for the Architect system and by Beckman Coulter for AU systems [31,32]. Important information not provided by both companies is the lot (a or b) of SRM 965 used to implement the traceability (SRM 965a has been out of stock for some years and since 2009 only SRM 965b has been available) [29]. Roche employs option B, exploiting the availability of their own reference laboratory performing the GC-IDMS procedure [33–35]. On the other hand, it seems that the type C chain is used by Siemens for Advia systems [36]. It is impossible to define the actual performance of a laboratory performing the CDC hexokinase reference procedure, as currently all accredited reference laboratory services for blood glucose measurement listed in the JCTLM

database use GC-IDMS. Finally, on the basis of what has been reported, it is likely that for Synchron systems, Beckman Coulter uses the type D chain [37]. Although it is possible to infer the different internal calibration hierarchies applied by different IVD companies, it is evident that there is incomplete information concerning the metrological traceability of commercial assays for blood glucose measurement. Indeed, often the highest reference of the traceability chain (which is always the NIST SRM 917) is not mentioned. In many cases only the reference material or procedure is indicated, when it would be appropriate to specify both, and, finally, none among surveyed companies distinguishes between primary and secondary reference materials.

Information about uncertainty is no better present. Beckman Coulter is, among evaluated companies, the only one that does not declare in the package inserts the uncertainty associated with calibrators for either of its automated systems. Abbott and Roche specify an uncertainty calculated in accordance with available guidelines [38,39]. Siemens states uncertainties, but without specifying whether they are expanded or which protocol was used to derive them. No company clearly specifies whether declared uncertainties are combined or not. However, comparing them with uncertainty values associated with higher-order references (last column of Table 1), it is possible to deduce that, with the possible exception of Abbott, they are all expanded u_c , that do not take into account the uncertainty accumulated in the earlier steps of trueness transfer. Moreover, Roche and Siemens report different uncertainty values for the same calibrator when used on different platforms (Integra vs. Cobas/Modular) or methods (hexokinase vs. glucose-oxidase). This is plausible if the calibrator value assignment proceeds according to the B and C patterns displayed in Fig. 3 that are possibly those used by these two companies [23].

Important information, never present in calibrator inserts, is the possible use of acceptable uncertainty limits. To ensure that glucose results of patient samples are clinically acceptable, by consensus the expanded u_c value associated with commercial calibrators should be $\leq 50\%$ of MG_U , i.e., $\leq 2.3\%$. By applying this goal and calculating the expanded u_c of commercial calibrators with the data presented in Table 1, it is possible to approximate the current state of the art of the glucose measurement. While the uncertainty of Abbott calibrator seems on the basis of the declared value (2.7%) already combined, it still does not meet the target of 2.3%. Considering the Roche systems, the uncertainties associated to the C.f.a.s. calibrator are 0.84% (Cobas c and Modular platforms) and 0.62% (Integra platform): if we add to these ones the uncertainty of glucose measurement obtained with GC-IDMS procedure performed by the same company, reported in the 2012 External Quality Assessment (EQA) for Reference Laboratories (RELA) [30], the expanded u_c associated with C.f.a.s. is between 1.8% and 1.9%, lower than the established minimum goal. Finally, for the calibrator used on Advia analytical platforms, the u values reported by Siemens are 0.65% for the hexokinase method and 0.40% for the glucose-oxidase one. Since there are no currently accredited reference laboratory services performing the CDC hexokinase reference procedure, we determined average values of uncertainty associated with samples of the panel used in the comparison study (Fig. 3C) from our center (CIRME) in the 2012 RELA exercise using as reference procedure the CDC hexokinase method [30]. The obtained expanded u_c of 1.9–2.0% is acceptable for both Advia methods at blood glucose concentrations around 13 mmol/L (2.35 g/L), while for physiologic glucose concentrations the expanded u_c of the calibrator is estimated around 3.3%, too high to fulfill the goal set at $1/2 MG_U$. Although these data are estimates in part, it seems that the expanded u_c values of commercial calibrators for glucose measurement, while heterogeneous, are such as to ensure, when added to the current imprecision of commercial systems, the achievement of MG_U .

In conclusion, the information regarding metrological traceability and uncertainty associated with commercial calibrators is currently very poor. Information such as the applied calibration hierarchy, the u_c associated with calibrator and the employed acceptable uncertainty limits, if any, is partly or totally missing.

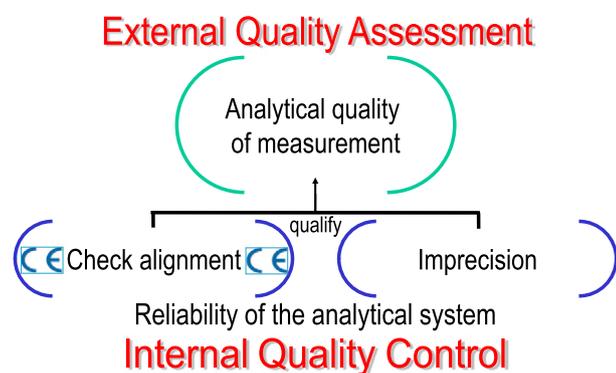


Fig. 4. The analytical quality control in the traceability era. Modified from ref. [2].

3.2. Daily surveillance of the IVD system traceability

Once a measurement system has been marketed and introduced into daily use, the possible sources of degradation of its performance, even in terms of traceability and uncertainty, are innumerable. It is therefore essential to carry out a careful post-marketing surveillance of the quality of performance of commercial assays and of the laboratory performing measurements in clinical practice. This surveillance relies substantially on the analytical quality control, which, however, must be reconsidered in terms that might appear revolutionary (Fig. 4) [2]. In particular, it is necessary to verify the consistency of the manufacturer's declared performance during routine operations performed strictly in accordance with the manufacturer's instructions (i.e. check the system alignment to the manufacturer's traceability chain), and to participate in EQA schemes structured so that they provide objective information on the analytical quality of measurements performed by participating laboratories.

The first activity consists in daily confirming the alignment of the analytical system as described in Fig. 2, checking that values of control materials provided by the manufacturer as component of the analytical system are in the established control range, with no clinically significant changes in the assumed unbiased results. Any "out of control" signal must be made available with sufficient time to allow immediate corrective actions to bring again the situation under control ("unbiased") and before reports related to the samples analyzed in the affected analytical run are issued.

The second tool useful to check the alignment of employed commercial systems to available higher-order references is the participation to EQA programs that meet specific metrological criteria. The requirements for the applicability of EQA results in the performance evaluation of participating laboratories in terms of standardization and traceability of measurements have been described in previous publications [2,9,40]. Briefly, in addition to the use of commutable control materials, it is necessary to assign values (and uncertainty) to them with reference procedures performed by an accredited laboratory and apply a clinically acceptable TEa limit. An example of the effectiveness of this approach has been recently provided for serum creatinine measurement in a national setting [41]. Unfortunately there are few EQA programs currently able to fulfill these requirements because of constraints including technical aspects (lack of certified control materials or inability to prepare commutable samples), practical considerations (difficulty of preparing samples covering the full measuring interval and the complicated logistics of preparation and distribution of fresh/frozen samples), psychological limitations (lack of awareness of which quality factors make an EQA important or an unwillingness to adopt them) and economic concerns [42]. The main purpose of an optimal EQA program must be to evaluate the analytical quality of laboratory measurements, including the traceability of the calibration and of patient results and the equivalence among laboratories for the obtained results. EQA schemes are therefore

in a unique position to add substantial value to the practice of Laboratory Medicine, by identifying analytes that need improved harmonization and by stimulating and sustaining standardization initiatives that are needed to support clinical practice guidelines [42].

4. Conclusion ("Act")

A few years ago, we wondered if the application of the metrological traceability theory in Laboratory Medicine represents a Copernican revolution or just an activity for a restricted professional group of subjects [43]. Today we are more and more convinced that it has a huge practical potential. However, paraphrasing Robert M. Pirsig, we can say that it will be only by the acceptance by clinical laboratories and our profession of a role of responsible verification of the correct application of the traceability theory that will "distinguish modern man from his medieval predecessors" [44]. The main aspects of the "traceability revolution manifesto" can be summarized as follows:

- definition and approval by JCTLM of reference measurement systems, possibly in their entirety;
- implementation by IVD industry of traceability to such reference systems in a scientifically sound and transparent way;
- adoption by providers of EQA programs of commutable materials and use of an evaluation approach exclusively based on accuracy;
- definition by the profession of the clinically acceptable measurement error for each of the analytes used in the clinical field;
- monitoring of the analytical performance of individual laboratories by the participation in appropriately structured EQA schemes and application of clinically acceptable limits;
- abandonment by users (and consequently by industry) of non-specific methods and/or of assays with demonstrated insufficient quality.

References

- [1] Panteghini M. Traceability, reference systems and result comparability. *Clin Biochem Rev* 2007;28:97–104.
- [2] Panteghini M. Application of traceability concepts to analytical quality control may reconcile total error with uncertainty of measurement. *Clin Chem Lab Med* 2010;48:7–10.
- [3] Directive 98/97/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. *Off J Eur Communities Dec 7 1998; L331:1–7.*
- [4] International Organization for Standardization (ISO) 17511:2003. In vitro diagnostic medical devices – measurement of quantities in biological samples – metrological traceability of values assigned to calibrators and control materials. Geneva: ISO; 2003.
- [5] International Organization for Standardization (ISO) 18153:2003. In vitro diagnostic medical devices – measurement of quantities in biological samples – metrological traceability of values for catalytic concentration of enzymes assigned to calibrators and control materials. Geneva: ISO; 2003.
- [6] Dati F. The new European Directive on in vitro diagnostics. *Clin Chem Lab Med* 2003;41:1289–98.
- [7] Panteghini M. Traceability as a unique tool to improve standardization in laboratory medicine. *Clin Biochem* 2009;42:236–40.
- [8] Panteghini M. Implementation of standardization in clinical practice: not always an easy task. *Clin Chem Lab Med* 2012;50:1237–41.
- [9] Braga F, Panteghini M. Standardization and analytical goals for glycated hemoglobin measurement. *Clin Chem Lab Med* 2013;51:1719–26.
- [10] Ceriotti F, Hinzmann R, Panteghini M. Reference intervals: the way forward. *Ann Clin Biochem* 2009;46:8–17.
- [11] Panteghini M, Ceriotti F. Obtaining reference intervals traceable to reference measurement systems: it is possible, who is responsible, what is the strategy? *Clin Chem Lab Med* 2012;50:813–7.
- [12] Weykamp CW, Mosca A, Gillery P, Panteghini M. The analytical goals for haemoglobin A_{1c} measurement in IFCC units and National Glycohemoglobin Standardization Program Units are different. *Clin Chem* 2011;57:1204–6.
- [13] Bais R, Armbruster D, Jansen RT, et al. Defining acceptable limits for the metrological traceability of specific measurands. *Clin Chem Lab Med* 2013;51:973–9.
- [14] Kallner A, McQueen M, Heuck C. The Stockholm Consensus Conference on quality specifications in laboratory medicine, 25–26 April 1999. *Scand J Clin Lab Invest* 1999;59:475–585.
- [15] Klee GG. Establishment of outcome-related analytic performance goals. *Clin Chem* 2010;56:714–22.

- [16] Panteghini M. Quality requirements for troponin assays – an overview. Troponin Monograph 2012. The Australasian Association of Clinical Biochemists Inc.; 2012. p. 53–61.
- [17] Fraser CG, Hyltoft Petersen P, Libeer JC, Ricos C. Proposals for setting generally applicable quality goals solely based on biology. *Ann Clin Biochem* 1997;34:8–12.
- [18] Kallner A. Measurement performance goals: how they can be estimated and a view to managing them. *Scand J Clin Lab Invest* 2010;70(Suppl. 242):34–9.
- [19] Stepman HC, Stöckl D, Twomey PJ, Thienpont LM. A fresh look at analytical performance specifications for biological variation. *Clin Chim Acta* 2013;421:191–2.
- [20] Clinical and Laboratory Standards Institute (CLSI). Metrological traceability and its implementation; a report. CLSI document X5-R. Wayne PA: Clinical and Laboratory Standards Institute; 2006.
- [21] Infusino I, Braga F, Mozzi R, Valente C, Panteghini M. Is the accuracy of serum albumin measurements suitable for clinical application of the test? *Clin Chim Acta* 2011;412:791–2.
- [22] Whicher JT. BCR/IFCC reference material for plasma proteins (CRM 470). *Clin Biochem* 1998;31:459–65.
- [23] Konnert A, Christoph Berding C, Arends S. Uncertainty calculation for calibrators and controls of laboratory diagnostic assays. *Clin Chem Lab Med* 2006;44:1175–82.
- [24] Merlini G, Bliurup-Jensen S, Johnson AM, Sheldon J, Zegers I, IFCC Committee on Plasma Proteins (C-PP). Standardizing plasma protein measurements worldwide: a challenging enterprise. *Clin Chem Lab Med* 2010;48:1567–75.
- [25] Infusino I, Panteghini M. Serum albumin: accuracy and clinical use. *Clin Chim Acta* 2013;419:15–8.
- [26] Franzini C, Ceriotti F. Impact of reference materials on accuracy in clinical chemistry. *Clin Biochem* 1998;31:449–57.
- [27] Infusino I, Braga F, Valente C, Panteghini M. Commutability of the ERM-DA470k reference material for two assays measuring serum albumin using immunochemical principles. *Clin Chem Lab Med* 2011;49:1383–4.
- [28] Infusino I, Mozzi R, Panteghini M. Imprecisione di alcuni metodi di misura dell'albumina derivata dai dati di un controllo di qualità interno. *Biochem Clin* 2008;32:217–8.
- [29] National Institute of Standards and Technology. Certificate of analysis. Standard reference material 965b. Glucose in frozen human serum. Certificate issue date ; December 01 2009.
- [30] http://www.dgkl-rfb.de:81/4Daction/g_search_RELselectAnalyte=Glucose&submitplot=show+result+plot&session_id=00000000000000000000&cur_year=2012&LabCode=000 . [Accessed August 7, 2013].
- [31] Abbott Diagnostics. Clinical chemistry traceability and uncertainty of measurement. Multiconstituent calibrator; January 2011.
- [32] Beckman Coulter. Beckman Coulter system calibrator L66300_0115_ML; 05 01 2011.
- [33] Roche Diagnostics GmbH, Centralized Diagnostics Operations, Quality Operations Penzberg. Traceability and uncertainty. Cobas C.f.a.s; August 2012.
- [34] Roche Diagnostics GmbH, Centralized Diagnostics Operations, Quality Operations Penzberg. Traceability and uncertainty. Cobas Integra C.f.a.s; August 2012.
- [35] Roche Diagnostics GmbH, Centralized Diagnostics Operations, Quality Operations Penzberg. Traceability and uncertainty. Roche/Hitachi C.f.a.s; March 2009.
- [36] Siemens Healthcare Diagnostics. Traceability and uncertainty of assigned calibrator and control values for Advia chemistry assays run on Advia chemistry systems . 10811244 Rev ; 02 2012.
- [37] Coulter Beckman. Synchron multicalibrator . A85956-AC ; 2011.
- [38] JCGM 100:2008. Evaluation of measurement data – guide to the expression of uncertainty in measurement 1st ed. ; 2008.
- [39] EURACHEM/CITAC. Guide quantifying uncertainty in analytical measurement. 2nd ed. Eurachem; 2000.
- [40] Infusino I, Schumann G, Ceriotti F, Panteghini M. Standardization in clinical enzymology: a challenge for the theory of metrological traceability. *Clin Chem Lab Med* 2010;48:301–7.
- [41] Carobene A, Ceriotti F, Infusino I, Frusciante E, Panteghini M. Evaluation of the impact of standardization process on the quality of serum creatinine determination in Italian laboratories. *Biochem Clin* 2012;37:414–24.
- [42] Miller WG, Jones GR, Horowitz GL, Weykamp C. Proficiency testing/external quality assessment: current challenges and future directions. *Clin Chem* 2011;57:1670–80.
- [43] Panteghini M. Traceability in laboratory medicine: Copernican revolution or activity for a restricted professional club? 4th International Scientific Meeting “Rethinking quality control in the traceability era”; November 30 2010 [Milano, Italy. Available at: <http://users.unimi.it/cirme/public/UploadAttach/Panteghini2010.pdf> (Accessed August 7, 2013)].
- [44] Pirsig RM. Zen and the art of motorcycle maintenance. New York: William Morrow & Company; 1974.