PD ISO/TS 20914:2019

BSI Standards Publication

Medical laboratories — Practical guidance for the estimation of measurement uncertainty

Documents
Document Sharing Hub

Full document details: PD ISO/TS 20914:2019

National foreword

This Published Document is the UK implementation of ISO/TS 20914:2019.

The UK participation in its preparation was entrusted to Technical Committee CH/212, IVDs.

A list of organizations represented on this committee can be obtained on request to its secretary.

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

© The British Standards Institution 2019
Published by BSI Standards Limited 2019

ISBN 978 0 539 01878 3

ICS 11.100.01

Compliance with a British Standard cannot confer immunity from legal obligations.

This Published Document was published under the authority of the Standards Policy and Strategy Committee on 31 August 2019.

Amendments/corrigenda issued since publication

Date	Text affected

Documents
Document Sharing Hub

Full document details: PD ISO/TS 20914:2019

TECHNICAL SPECIFICATION

ISO/TS 20914

First edition
2019-07

Medical laboratories — Practical guidance for the estimation of measurement uncertainty

Laboratoires médicaux — Lignes directrices pratiques pour l'estimation de l'incertitude de mesure

Reference number
ISO/TS 20914:2019(E)

Documents
Document Sharing Hub
© ISO 2019

Full document details: PD ISO/TS 20914:2019

COPYRIGHT PROTECTED DOCUMENT

© ISO 2019

All rights reserved. Unless otherwise specified, or required in the context of its implementation, no part of this publication may be reproduced or utilized otherwise in any form or by any means, electronic or mechanical, including photocopying, or posting on the internet or an intranet, without prior written permission. Permission can be requested from either ISO at the address below or ISO's member body in the country of the requester.

ISO copyright office
CP 401 • Ch. de Blandonnet 8
CH-1214 Vernier, Geneva
Phone: +41 22 749 01 11
Fax: +41 22 749 09 47
Email: copyright@iso.org
Website: www.iso.org

Published in Switzerland

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub

Full document details: PD ISO/TS 20914:2019

Contents

Page

Foreword ..... **iv**
Introduction ..... **v**
1 Scope **1**
2 Normative references **1**
3 Terms and definitions **1**
4 Abbreviated terms and symbols **13**
5 Measurement uncertainty for medical laboratories **13**
5.1 Measurement uncertainty concept 13
5.2 Maximum allowable measurement uncertainty 16
5.3 Sources of measurement uncertainty 17
5.4 Expression of measurement uncertainty 18
5.5 Use of relative standard uncertainty for calculating uncertainty estimates 21
5.6 Reporting measurement uncertainty 22
6 Steps for estimating uncertainty of measurand values **22**
6.1 Measurand definition 22
6.2 Measurement precision 24
6.3 Effect of reagent and internal quality control lot changes on estimating uncertainty 24
6.4 Laboratories using multiple measuring systems for the same measurand 25
6.5 Uncertainty of end-user calibrator values (u_{cal}) 25
6.6 Measurement bias 26
6.7 Process overview for estimation of measurement uncertainty 26
6.8 Re-estimation of measurement uncertainty 27
6.9 Qualitative results based on numerical results 27
6.10 Uncertainty of counting entities 28
6.11 Limitations of measurement uncertainty estimates 28
Annex A (informative) **Worked examples of estimating measurement uncertainty** **29**
Annex B (informative) **Example of applying measurement uncertainty to result interpretation** **58**
Annex C (informative) **Supplementary information on some aspects of uncertainty** **60**
Bibliography **71**

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular, the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and in vitro diagnostic test systems*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

Introduction

Improved standardization and harmonization of medical laboratory practices worldwide benefits society as patients and healthcare professionals increasingly move within and between healthcare services in the global economy. To help achieve the objective of improved standardization among medical laboratories, ISO 15189 focuses on the application of the quality systems approach in the medical laboratory. Since the first version of ISO 15189 was published in 2003, this international standard has been increasingly adopted worldwide as a desirable (and in some cases mandatory) quality system standard for medical laboratories.

To ensure that measurement results are useful and safe in medical practice and to permit meaningful comparison with medical decision limits and previous results of the same kind in the same individual, medical laboratories require estimates for the overall variability in values reported by their measurement procedures. To achieve this, ISO 15189:2012, 5.5.1.4, requires that "…(medical laboratories)… shall determine measurement uncertainty for each measurement procedure in the examination phase used to report measured quantity values on patients' samples." Additionally, "Upon request, the laboratory shall make its estimates of measurement uncertainty available to laboratory users."

For medical laboratories and healthcare providers, measurement uncertainty (MU) estimates:

— indicate that multiple values are possible for a given measurement;

— provide evidence that the term 'true value' of a quantity is a theoretical concept;

— quantify the quality of a result relative to its suitability for use in making medical decisions;

— assume that known medically significant bias is eliminated;

— assist in identifying technical steps to reduce MU;

— allow combination with other sources of uncertainty;

— can be used to determine if medically allowable analytical performance specifications can be achieved;

— support interpretation of patient results close to medical decision limits.

To enable fulfilment of the requirement of ISO 15189 for estimation of MU, it is essential that medical laboratories be provided with a coherent, standardized, and best practice approach to the terminology, principles and statistical methods required for estimation of MU. *Evaluation of measurement data — Guide to the expression of uncertainty in measurement* (GUM) JCGM 100:2008, a definitive reference on the topic of MU, provides in-depth information regarding the mathematical and metrological considerations appropriate for a detailed estimation of elements to be considered in the estimation of MU for a broad range of measuring systems, across many disciplines in science and engineering. In the Scope, GUM subclause 1.2, states that "This document is primarily concerned with the expression of uncertainty in the measurement of a well-defined physical quantity that can be defined by an essentially unique value." GUM, Scope subclause 1.4, goes on to say that "…(GUM) provides general rules for evaluating and expressing uncertainty in measurement rather than detailed, technology-specific instructions. (GUM) … does not discuss how the uncertainty of a particular measurement result, once evaluated, may be used for different purposes, for example, to draw conclusions about the compatibility of that result with other similar results, to establish tolerance limits in a manufacturing process, or to decide if a certain course of action may be safely undertaken. Therefore, it may be necessary to develop particular standards based on (GUM) that deal with the problems peculiar to specific fields of measurement or with the various uses of quantitative expressions of uncertainty. These standards may be simplified versions of (GUM) but should include the detail that is appropriate to the level of accuracy and complexity of the measurements and uses addressed."

This document is therefore concerned with practical approaches to estimation of MU, to be applied in medical laboratory settings for the purpose of estimating MU of values produced by measurement procedures intended to measure a broad range of biological measurands. The measurands of interest

AVA Documents
Document Sharing Hub

© ISO 2019 – All rights reserved

Full document details: PD ISO/TS 20914:2019

are subject to measurement for the purpose of providing medical diagnostic information to health care practitioners and are typically present in complex biological fluid and tissue matrices. In contemporary medical laboratory settings, the vast majority of these measurements are performed with commercial devices, including automated instrumentation and packaged reagent kits. Characterization of the performance of these measurement procedures in an end-user laboratory environment is typically limited to the gathering of empirical performance data using surrogate quality control samples designed to emulate the intended patient samples. Such data, commonly known as internal quality control (IQC) data, may be appropriate for characterization of repeatability and long-term imprecision of a given measurement procedure. Additional uncertainty information regarding higher order elements of the calibration hierarchy for a given measurement procedure should be available from the manufacturer, and should be accounted for in the medical laboratory's process for estimation of MU. As such, a GUM top down approach is appropriate, and a particular application for use in medical laboratories is outlined in Clause 6.

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

Medical laboratories — Practical guidance for the estimation of measurement uncertainty

1 Scope

This document provides practical guidance for the estimation and expression of the measurement uncertainty (MU) of quantitative measurand values produced by medical laboratories. Quantitative measurand values produced near the medical decision threshold by point-of-care testing systems are also included in this scope. This document also applies to the estimation of MU for results produced by qualitative (nominal) methods which include a measurement step. It is not recommended that estimates of MU be routinely reported with patient test results, but should be available on request.

NOTE See Annex B for an example of application of the MU.

2 Normative references

There are no normative references in this document.

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
analyte
component represented in the name of a measurand

Note 1 to entry: Constituent of a sample with a measurable property.

EXAMPLE In the measurand (measured quantity) "mass of total protein in 24-hour urine", "total protein" is the analyte (and “mass” is the property.) In "amount of substance concentration of glucose in plasma", "glucose" is the analyte (and “amount of substance concentration” is the property.)

[SOURCE: ISO 18113-1:2009, modified]

Note 2 to entry: JCGM 200:2012, 5.4, states that a primary measurement standard may be “…prepared by dissolving a known amount of substance of a chemical component to a known volume of solution”.

3.2
calibration
operation that, under specified conditions, in a first step, establishes a relation between the quantity values with associated measurement uncertainties provided by measurement standards (calibrators) and their corresponding indications and, in a second step, uses this relationship to establish a measurement result from an indication (for an unknown sample).

Note 1 to entry: A calibration may be expressed by a statement, calibration function, calibration diagram, calibration curve, or calibration table. In some cases, it may consist of an additive or multiplicative correction of the indication with associated MU.

Note 2 to entry: Calibration should not be confused with adjustment of a measuring system, often mistakenly called “self-calibration”, nor with verification of calibration.

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

Note 3 to entry: Often, the first step alone in the above definition is perceived as being calibration.

[SOURCE: JCGM 200:2012, 2.39, modified]

3.3
calibrator
measurement standard used in calibration

[SOURCE: JCGM 200:2012, 5.12]

Note 1 to entry: In this document, calibrator is synonymous with calibration material.

Note 2 to entry: A calibrator is a measurement standard used in the calibration of a measuring system according to a specified measurement procedure.

3.4
commutability of a reference material
property of a reference material, demonstrated by the closeness of agreement between the relation among the measurement results for a stated quantity in this material, obtained according to two measurement procedures, and the relation obtained among the measurement results for other specified materials

Note 1 to entry: The reference material in question is usually a calibrator and the other specified materials are usually routine samples.

[SOURCE: JCGM 200:2012, 5.15]

Note 2 to entry: It is typical that there are more than two measurement procedures available and comparison among all applicable measurement procedures is desirable.

Note 3 to entry: The requirement for the closeness of agreement shall be appropriate for the intended use of the reference material.

Note 4 to entry: The commutability statement is restricted to the measurement procedures as specified in a particular comparison.

3.5
component
constituent of a mixture the amount or concentration of which can be varied independently

[SOURCE: International Union of Pure and Applied Chemistry (IUPAC) Compendium of Chemical Terminology (Gold Book) Version 2.3.3 2014-02-24, modified]

Note 1 to entry: See also *analyte* (3.1).

3.6
coverage factor
k
number larger than one by which a standard uncertainty value (u) is multiplied to obtain an *expanded uncertainty*, U (3.9)

Note 1 to entry: A coverage factor is usually symbolized k.

[SOURCE: JCGM 200:2012, 2.38, modified]

3.7
coverage interval
interval containing the set of true quantity values of a measurand with a stated probability, based on the information available

Note 1 to entry: A coverage interval does not need to be centred on the chosen measured quantity value (see JCGM 101:2008).

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

Note 2 to entry: A coverage interval should not be termed "confidence interval" to avoid confusion with the statistical concept (see GUM:1995, 6.2.2).

Note 3 to entry: A coverage interval can be derived from an expanded MU (see GUM:1995, 2.3.5).

[SOURCE: JCGM 200:2012, 2.36]

Note 4 to entry: The term 'true' is considered redundant by GUM. For this document the term 'value of the measurand' is used.

3.8
end-user calibrator
end-user in vitro diagnostic medical device (IVD MD) calibrator
reference material used as a measurement standard (calibrator) intended for use with one or more measurement procedures intended to examine a particular measurand in human samples

3.9
expanded measurement uncertainty
U
expanded uncertainty
(multiplication) product of a u by a (coverage) factor k larger than the number one

[SOURCE: JCGM 200:2012, 2.35, modified]

Note 1 to entry: A measured value $x \pm [k \times u(y)]$, with coverage factor $k = 2$, means that the laboratory believes (≈95 % level of confidence) that the value of the measurand lies in the interval of values defined by the following formula:

$$x \pm \left[k \times u(y)\right]$$

where

X	is the measured value;
K	is the coverage factor (usually 2 for ≈95 % confidence);
$u(y)$	is the standard uncertainty of a measured value, y.

3.10
external quality assessment
EQA
international, national or local program designed to provide regular, external, independent quality assessment of a medical laboratory's analytical performance, and assist in detecting bias of reported results compared to other laboratories.

Note 1 to entry: Also known as Proficiency Testing (PT)[19-21].

Note 2 to entry: EQA is the term used in this document.

3.11
indication
quantity value provided by a measuring instrument or a measuring system

Note 1 to entry: An indication may be presented in visual or acoustic form or may be transferred to another device. An indication is often given by the position of a pointer on the display for analog outputs, a displayed or printed number for digital outputs, a code pattern for code outputs, or an assigned quantity value for material measures.

[SOURCE: JCGM 200:2012, 4.1]

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

3.12
intermediate precision condition of measurement
condition of measurement, out of a set of conditions that includes the same measurement procedure, same location, and replicate measurements on the same or similar objects over an extended period of time, but may include other conditions involving changes

Note 1 to entry: The changes can include new calibrations, calibrators, operators, and measuring systems.

Note 2 to entry: A specification for the conditions should contain the conditions changed and unchanged, to the extent possible.

[SOURCE: JCGM 200:2012, 2.22]

Note 3 to entry: For this document, the term long-term precision (u_{Rw}) is used to mean precision data for a given measurement procedure obtained over an extended period of time that at some point includes the effects of all or most changes in measuring conditions, for example, consumable lot changes, re-calibrations, etc. Such changes should be defined for each measurement procedure [see 3.33 repeatability condition of measurement (JCGM 200:2012, 2.20); see 3.40 uncertainty component under conditions of within-laboratory precision (u_{Rw})].

Note 4 to entry: Changed conditions may include instrument maintenance where appropriate.

Note 5 to entry: u_{Rw} is often the major contributor to the combined standard uncertainty of a measurement result in the medical laboratory.

3.13
internal quality control
IQC
set of procedures and specified materials used by laboratory staff for the repetitive monitoring of analytical performance of measuring systems

3.14
long-term precision
u_{Rw}
see 3.12, 3.40

Note 1 to entry: Both the term 'long-term precision' and the symbol u_{Rw} are used in this document when refering to an uncertainty estimate based on data observed under intermediate precision conditions of measurement.

3.15
maximum allowable measurement uncertainty
target measurement uncertainty
maximum fit for purpose MU for measurement results produced by a given measurement procedure, and specified as an upper limit based on an evaluation of medical requirements

[SOURCE: JCGM 200:2012, 2.34 and 4.26, modified]

Note 1 to entry: JCGM 200:2012, 4.26, defines maximum permissible measurement error. In modern English usage, the difference between the terms 'allowed' and 'permitted' is analogous to the difference between the concepts of tolerance (allowed) and authorization (permitted). Authorization implies a statutory, mandated, or legal requirement. For most measurands in laboratory medicine there are no legal limits of performance, therefore allowable is the preferred adjective in the context of this definition.

Note 2 to entry: The maximum allowable MU is considered to represent fit-for-purpose performance based on use of a measurement result for a medical decision.

3.16
measurand
quantity intended to be measured

Note 1 to entry: Specification of a measurand requires knowledge of the kind of quantity, description of the state of the phenomenon, body, or substance carrying the quantity, including any relevant component, and the chemical entities involved.

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

Note 2 to entry: In the second edition of the VIM and in IEC 60050-300:2001, the measurand is defined as the "particular quantity subject to measurement".

Note 3 to entry: The measurement, including the measuring system and the conditions under which the measurement is carried out, might change the phenomenon, body, or substance such that the quantity being measured may differ from the measurand as defined. In this case, adequate correction is necessary.

EXAMPLE The length of a steel rod in equilibrium at ambient Celsius temperature of 23 °C will be different from the length at the specified temperature of 20 °C, which is the measurand. In this case, a correction is necessary.

Note 4 to entry: In chemistry, 'analyte', or the name of a substance or compound, are terms sometimes used for 'measurand'. This usage is erroneous because these terms do not refer to quantities.

[SOURCE: JCGM 200:2012, 2.3]

Note 5 to entry: In laboratory medicine, the description of the measurand includes the name of the quantity (e.g. amount of substance concentration), the component/analyte (e.g. β-D-glucose), and the biological system in which it is found (e.g. blood plasma.)

[SOURCE: ISO 18113-1:2009, 3.39]

3.17
measurement
process of experimentally obtaining one or more quantity values that can be reasonably attributed to a quantity

Note 1 to entry: Measurement does not apply to nominal properties.

Note 2 to entry: Measurement implies comparison of quantities or counting of entities.

Note 3 to entry: Measurement presupposes a description of the quantity commensurate with the intended use of a measurement result, a measurement procedure, and a calibrated measuring system operating according to the specified measurement procedure, including the measurement conditions.

[SOURCE: JCGM 200:2012, 2.1]

Note 4 to entry: A measurand is the quantity intended to be measured by a medical laboratory. See 3.17.

3.18
measurement bias
estimate of a systematic measurement error

[SOURCE: JCGM 200:2012, 2.18]

Note 1 to entry: Difference between the accepted value of a commutable reference material and the mean value of replicate measurements produced under repeatability conditions by a medical laboratory measurement procedure

Note 2 to entry: Difference between the mean value of replicate measurements produced by a reference measurement procedure and the mean value of replicate measurements produced under repeatability conditions by a medical laboratory measurement procedure.

Note 3 to entry: Because of measurement imprecision, values for measurement bias cannot be exactly known.

3.19
measurement error
measured quantity value minus a reference quantity value

[SOURCE: JCGM 200:2012, 2.16]

Note 1 to entry: In general, a measurement has imperfections that give rise to an error in the measurement result. Traditionally, an error is viewed as having two components, namely, a random component and a systematic component.

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

Note 2 to entry: Error is an idealized concept and errors cannot be known exactly.

[SOURCE: JCGM 100:2008; 3.2.1, Notes 1 and 2]

3.20
measurement method
generic description of a logical organization of operations used in a measurement

Note 1 to entry: Measurement methods may be qualified in various ways such as:

— substitution measurement method;

— differential measurement method;

— null measurement method;

— direct measurement method;

— indirect measurement method.

Note 2 to entry: See IEC 60050-300:2001.

[SOURCE: JCGM 200:2012, 2.5]

3.21
measurement precision
precision
closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions

Note 1 to entry: Measurement precision is usually expressed numerically by measures of imprecision, such as variance, standard deviation (SD), or coefficient of variation (C_V) under the specified conditions of measurement.

Note 2 to entry: The 'specified conditions' can be, for example, repeatability conditions of measurement, intermediate precision conditions of measurement, or long-term conditions of measurement (see ISO 5725-1:1994).

Note 3 to entry: Measurement precision is used to define measurement repeatability, intermediate measurement precision, and long-term measurement imprecision.

[SOURCE: JCGM 200:2012, 2.15]

Note 4 to entry: Imprecision denotes the statistical measure or metric related to the degree of closeness or dispersion, such as SD, CV, range, etc. In this context, a measurement procedure is of good precision when the imprecision is low, and of bad precision when the imprecision is high relative to the precision needed to make medical decisions based on the value of the quantity measured.

3.22
measurement procedure
detailed description of a measurement according to one or more measurement principles and to a given measurement method, based on a measurement model and including any calculation to obtain a measurement result

Note 1 to entry: A measurement procedure is usually documented in sufficient detail to enable a competent operator to perform a measurement.

[SOURCE: Modified – added "competent"]

Note 2 to entry: A measurement procedure can include a statement concerning a target MU.

Note 3 to entry: A measurement procedure is sometimes called a standard operating procedure, abbreviated SOP.

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

[SOURCE: JCGM 200:2012, 2.6]

Note 4 to entry: Target MU as described in Note 2 of JCGM 200:2012, 2.6, is referred to as maximum allowable measurement uncertainty in this document. See 3.15.

3.23
measurement repeatability
measurement precision under a set of repeatability conditions of measurement

[SOURCE: JCGM:200:2012, 2.21]

Note 1 to entry: See 3.33.

3.24
measurement result
set of quantity values being attributed to a measurand together with any other available relevant information

Note 1 to entry: A measurement result generally contains 'relevant information' about the set of quantity values, such that some may be more representative of the measurand than others. This may be expressed in the form of a probability density function (PDF).

Note 2 to entry: A measurement result is generally expressed as a single measured quantity value and a MU. If the MU is considered to be negligible for some purpose, the measurement result may be expressed as a single measured quantity value. In many fields, this is the common way of expressing a measurement result.

[SOURCE: JCGM 200:2012, 2.9]

3.25
measurement standard
realization of the definition of a given quantity, with stated quantity value and associated MU, used as a reference

EXAMPLE 1 1 kg mass measurement standard with an associated u of 3 µg.

EXAMPLE 2 Set of reference solutions of cortisol in human serum having a certified quantity value with MU for each solution.

EXAMPLE 3 Reference material providing quantity values with measurement uncertainties for the mass concentration of each of ten different proteins.

Note 1 to entry: A "realization of the definition of a given quantity" can be provided by a measuring system, a material measure, or a reference material.

Note 2 to entry: A measurement standard (calibrator) is frequently used as a reference in establishing measured quantity values and associated MU for other quantities of the same kind, thereby establishing metrological traceability through calibration of other measurement standards, measuring instruments, or measuring systems.

Note 3 to entry: The term "realization" is used here in the most general meaning. It denotes three procedures of "realization". The first one consists in the physical realization of the measurement unit from its definition and is realization sensu stricto. The second, termed "reproduction", consists not in realizing the measurement unit from its definition but in setting up a highly reproducible measurement standard based on a physical phenomenon, as it happens, e.g. in case of use of frequency-stabilized lasers to establish a measurement standard for the metre, of the Josephson effect for the volt or of the quantum Hall effect for the ohm. The third procedure consists in adopting a material measure as a measurement standard. It occurs in the case of the measurement standard of 1 kg.

Note 4 to entry: A standard MU associated with a measurement standard is always a component of the combined standard MU (See JCGM 100:2008, 2.3.4) in a measurement result obtained using a procedure calibrated with the measurement standard. Frequently, this component is smaller when compared with other components of the combined standard MU.

Note 5 to entry: Quantity value and MU must be determined at the time when the measurement standard is used.

Note 6 to entry: Several quantities of the same kind or of different kinds may be realized in one device which is commonly also called a measurement standard.

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

Note 7 to entry: The word "embodiment" is sometimes used in the English language instead of "realization".

Note 8 to entry: In science and technology, the English word "standard" is used with at least two different meanings: as a specification, technical recommendation, or similar normative document (in French « norme ») and as a measurement standard (in French « étalon »). This vocabulary is concerned solely with the second meaning.

[SOURCE: JCGM 200:2012, 5.1]

3.26
measurement uncertainty
MU
parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used.

Note 1 to entry: MU includes components arising from systematic effects, as in the case of corrections to the assigned quantity values of measurement standards. Sometimes estimated systematic effects are not corrected for, but instead, the associated MU components are incorporated.

Note 2 to entry: The parameter may be, for example, a SD called standard MU (or a specified multiple of it), or the half-width of an interval, having a stated coverage probability.

Note 3 to entry: MU comprises, in general, many components. Some of these may be evaluated by Type A evaluation of MU from the statistical distribution of the quantity values from series of measurements and can be characterized by SD. The other components, which may be evaluated by Type B evaluation of MU, can also be characterized by SD or evaluated from probability density functions based on experience or other information.

Note 4 to entry: In general, for a given set of information, it is understood that the MU is associated with a stated quantity value attributed to the measurand. A modification of this value results in a modification of the associated uncertainty.

[SOURCE: JCGM 200:2012, 2.26]

Note 5 to entry: All measurements have bias and imprecision. For example, replicate measurements of a sample performed under repeatability conditions generally produce different values for the same measurand. Because the different values could all be reasonably attributed to the same amount of measurand, there is uncertainty as to which value should be reported as the value of the measurand.

Note 6 to entry: Based on available data about the analytical performance of a given measurement procedure, an estimation of MU provides an interval of values that is believed to include the actual value of the measurand, with a stated level of confidence.

Note 7 to entry: Available data about the analytical performance of a given measurement procedure typically comprise uncertainty of calibrator assigned values and long-term imprecision of IQC materials.

Note 8 to entry: In medical laboratories, most measurements are performed in singleton, and are taken to be an acceptable estimate of the value of the measurand, while the MU interval indicates other results that are also possible.

3.27
measuring system
set of one or more measuring instruments and often other devices, including any reagent and supply, assembled and adapted to give information used to generate measured quantity values within specified intervals for quantities of specified kinds.

Note 1 to entry: A measuring system may consist of only one measuring instrument.

[SOURCE: JCGM 200:2012, 3.2]

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

3.28
metrological traceability
property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the MU

Note 1 to entry: For this definition, a 'reference' can be a definition of a measurement unit through its practical realization, or a measurement procedure including the measurement unit for a non-ordinal quantity, or a measurement standard.

Note 2 to entry: Metrological traceability requires an established calibration hierarchy.

Note 3 to entry: Specification of the reference must include the time at which this reference was used in establishing the calibration hierarchy, along with any other relevant metrological information about the reference, such as when the first calibration in the calibration hierarchy was performed.

Note 4 to entry: For measurements with more than one input quantity* in the measurement model, each of the input quantity values should itself be metrologically traceable and the calibration hierarchy involved may form a branched structure or a network. The effort involved in establishing metrological traceability for each input quantity value should be commensurate with its relative contribution to the measurement result.

Note 5 to entry: JCGM 200:2012, 2.50 defines input quantity in a measurement model as the quantity that must be measured, or a quantity the value of which can be otherwise obtained, in order to calculate a measured quantity value of a measurand. Example: length of a steel rod at a specified temperature is the measurand, while the ambient temperature, the observed length of the steel rod, and the thermal expansion coefficient of the steel rod are the input quantities in the measurement model.

Note 6 to entry: Metrological traceability of a measurement result does not ensure that the MU is adequate for a given purpose or that there is an absence of mistakes in metrological traceability implementation.

Note 7 to entry: A comparison between two measurement standards may be viewed as a calibration if the comparison is used to check and, if necessary, correct the quantity value and MU attributed to one of the measurement standards.

Note 8 to entry: The International Laboratory Accreditation Cooperation (ILAC) considers the elements for confirming metrological traceability to be an unbroken metrological traceability chain to an international measurement standard or a national measurement standard, a documented MU, a documented measurement procedure, accredited technical competence, metrological traceability to the SI, and calibration intervals (see ILAC P-10:2002).

Note 9 to entry: The abbreviated term "traceability" is sometimes used to mean 'metrological traceability' as well as other concepts, such as 'sample traceability' or 'document traceability' or 'instrument traceability' or 'material traceability', where the history ("trace") of an item is meant. Therefore, the full term of "metrological traceability" is preferred if there is any risk of confusion.

[SOURCE: JCGM 200:2012, 2.41]

3.29
proficiency testing
PT
also known as External Quality Assessment (EQA)

Note 1 to entry: See 3.10.

3.30
property
attribute of a substance, body or phenomenon e.g. color, nucleotide sequence, length, mass, light emission wavelength

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

3.31
quantity
property of a phenomenon, body, or substance, where the property has a magnitude that can be expressed as a number and a reference

Note 1 to entry: The preferred IUPAC-IFCC format for designations of quantities in laboratory medicine is "*System — Component; kind-of-quantity*".

EXAMPLE 1 "Plasma (Blood) - Sodium ion; amount-of-substance concentration equal to 143 mmol/l in a given person at a given time".

[SOURCE: JCGM 200:2012, 1.1]

EXAMPLE 2 Number concentration of erythrocytes in blood sample (Whole Blood – erythrocytes; number concentration equal to 5×10^6/µl in a given person at a given time).

Note 2 to entry: "Quantity" is not to be confused with "analyte", see 3.1.

Note 3 to entry: Measurement procedures for which the measurement is expressed in a qualitative manner (e.g. "present" or "not present") against a ratio or counting scale with a pre-determined decision threshold, are consistent with this definition of the term quantity.

3.32
relative standard measurement uncertainty
u_{rel}
standard measurement uncertainty (u) divided by the absolute value of the measured quantity value

[SOURCE: JCGM 200:2012, 2.32]

Note 1 to entry: This general calculation is commonly termed a coefficient of variation (C_V).

Note 2 to entry: In this document, relative standard measurement uncertainty (u_{rel}) is used to distinguish it from other uses of CV.

3.33
repeatability condition of measurement
condition of measurement, out of a set of conditions that includes the same measurement procedure, same operator, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time

[SOURCE: JCGM 200:2012, 2.20]

Note 1 to entry: A repeatability study is usually conducted when verifying the analytical performance characteristics of a measurement procedure before introduction to service as it indicates the best precision achievable in the hands of the laboratory. A repeatability study may also be performed if an apparent bias of an in-service measurement procedure based on minimal replication requires further evaluation.

3.34
selectivity of a measuring system
property of a measuring system, used with a specified measurement procedure, whereby it provides measured quantity values for one or more measurands such that the values of each measurand are independent of other measurands or other quantities in the phenomenon, body, or substance being investigated

EXAMPLE 1 Capability of a measuring system to measure the amount-of-substance concentration of creatinine in blood plasma without being influenced by the other components present in the sample.

Note 1 to entry: In chemistry, selectivity of a measuring system is usually obtained for quantities with selected components in concentrations within stated intervals.

Note 2 to entry: Selectivity as used in physics is a concept close to specificity as it is sometimes used in chemistry.

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

[SOURCE: JCGM 200:2012, 4.13, modified]

EXAMPLE 2 Capability of a measuring system to measure the amount-of-substance concentration of creatinine in blood plasma by a Jaffé procedure without being influenced by the glucose, urate, ketone and protein concentrations.

3.35
standard deviation
SD
<for a series of measurements of the same measurand> quantity characterizing the dispersion of the results

[SOURCE: JCGM 100:2008, B.2.17, modified]

Note 1 to entry: A measure of the variability (dispersion or spread) of any set of numerical values about their arithmetic mean (average), defined as the positive square root of the variance.

Note 2 to entry: Quantitative measure of the variation or dispersion of values, from the same process, about the true but unknown value.

Note 3 to entry: SD, as used in this document, refers to long-term precision (see 3.21).

Note 4 to entry: SDs are used in many different situations to quantify the dispersion of values of different types of data sets. In the context of MU, the SD quantifying the dispersion of quantity values obtained from precision studies under repeatability or long-term precision conditions is termed standard MU (u) to distinguish it from other applications of SD.

Note 5 to entry: SDs cannot be added or subtracted. Such calculations require use of variances (see 3.39).

3.36
standard error
SE
quantitative measure of the variation or dispersion of sample means or sample averages

Note 1 to entry: Sometimes known as SD of the mean.

Note 2 to entry: A value of a measurand for example in a reference material requires calculation of a mean value using a small number of measured values obtained under repeatability conditions. If the repeatability study were to be repeated many times slightly different mean values would be obtained, so that the mean value also has a MU. Instead of performing multiple repeatability studies, the u of the mean value obtained from a single repeatability study can be quantified by calculating [see formula] the SD of the mean value (SD_{mean}):

$$SD_{mean} = SD / \sqrt{n}$$

where

SD_{mean} is calculated by dividing the SD of the n contributing observations in the series (from a repeatability study) by the square root of n.

EXAMPLE To evaluate the bias of a serum creatinine measurement procedure, a reference material for serum creatinine was measured 20 times under repeatability conditions.

Mean value 122,0 µmol/l, SD 0,63 µmol/l; n = 20

SD_{mean} = 0,63/√20 = u = 0,15 µmol/l, U = 0,30, k = 2

Note 3 to entry: The expanded uncertainty, U, for the creatinine concentration in the reference material (with a mean value of 122,0 µmol/l) as measured by an end-user measurement procedure is: 122,0 ± 0,30 µmol/l (≈95 % level of confidence). It should be noted that the measurand values assigned to higher order reference materials also have stated uncertainties provided with their certificates that must be combined with the u of the mean value obtained as described above to correctly estimate the MU of the end-user measurement procedure.

Note 4 to entry: It can be seen that as n increases, the SD_{mean} decreases, providing a more reliable estimate of the mean value of the measurand in the reference material.

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

3.37
standard measurement uncertainty
u
standard uncertainty
measurement uncertainty expressed as a standard deviation

[SOURCE: JCGM 200:2012, 2.30]

Note 1 to entry: A value for *u* is non-negative i.e. stated without a sign, for example 0,14 mmol/l. See also 3.40.

3.38
trueness
closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value

[SOURCE: JCGM 200:2012, 2.14]

3.39
variance
square of the standard deviation (SD^2; u^2)

Note 1 to entry: Sufficient measurement results obtained from precision studies are dispersed in a way that generally approximates a Gaussian distribution. Like SD, variance (SD^2; u^2) is a statistical parameter of how far individual values are spread out from the mean value of all the contributing results. While the SD is the average distance from the mean value, the variance is the average of the squared distance to the mean value. A low variance means contributing values are close to the mean and to each other, while a high variance means values are far from the mean and from each other.

Note 2 to entry: The spread of values typically obtained from performing replicate measurements under repeatability or intermediate precision studies using IQC materials can be characterised by variance. Variance is calculated per formula below as the sum of the squares of the difference of each individual value from the mean value, divided by the degrees of freedom (total number of values minus one):

$$SD^2 = \left[\Sigma\left(x-\bar{x}\right)^2\right] / n-1$$

Note 3 to entry: The measurement unit of variance is impractical for laboratory use because its measurement unit is the square of the measurement unit applicable to the data (see 3.35). For laboratory calculation purposes, variance must first be converted either to a SD or to a standard uncertainty (*u*), calculated by the following formula:

$$SD = \sqrt{SD^2} \text{ or } u = \sqrt{u^2}$$

so that the dispersion of measurand values can be expressed in the same measurement unit.

Note 4 to entry: SD or *u* values cannot be added or subtracted. Such calculations using independent standard uncertainties (*u*) or relative standard uncertainties (u_{rel}) require the values to first be converted to their respective variances (SD^2; CV^2), and then summed per Formula (1):

$$\text{estimated total variance} = \left(u^2{}_1 + u^2{}_2 + \ldots u^2{}_n\right) \quad (1)$$

Once the total variance is calculated per Formula (1), the estimated total (combined) standard uncertainty is calculated per Formula (2):

$$\text{estimated total standard uncertainty}, u\left(y\right) = \sqrt{\ } \text{ total variance [from Formula (1)]}$$

(2)

Similarly, the total relative variance may be calculated per Formula (3):

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

$$\text{total relative variance} = (u_1 / \text{value}_1)^2 + (u_2 / \text{value}_2)^2 + \ldots (u_n / \text{value}_n)^2 \quad (3)$$

and total relative standard uncertainty (u_{rel}) is calculated per Formula (4):

$$u_{rel} = \sqrt{\text{total relative variance. [from Formula (3)]}} \quad (4)$$

For worked examples see A.2.4.

3.40
uncertainty component under conditions of within-laboratory precision
u_{Rw}
estimate of standard uncertainty for a given measuring system in the same laboratory over an extended time period that includes routine changes to measuring conditions, for example, lot changes of reagents, calibrators, instrument maintenance

Note 1 to entry: Also termed long-term precision (which is used in this document; see 3.12, 3.21, 3.23)

4 Abbreviated terms and symbols

k	coverage factor applied to u to obtain an expanded confidence interval U
SD_{mean}	standard deviation of the mean value of a measurand obtained from a repeatability study. Taken to be the uncertainty of measured value y of measurand Y
u	measurement uncertainty expressed as a standard deviation
u_{bias}	u of a bias value
u_{cal}	u of the value assigned to an end-use calibrator
u_{ref}	u of the value assigned to a reference material
u_{Rw}	u for long-term imprecision of measured values obtained under defined conditions in same laboratory for a period sufficient to include all routine changes to measuring conditions, e.g., different lots of reagents, operators, and environmental conditions.
$u_{rel}(y)$	relative u of a measured value y [$u(y)/y$]; also expressed as a percentage % $u_{rel}(y)$. Used in this guide to distinguish from other uses of CV
$U_{rel}(y)$	relative expanded uncertainty of measured value y of measurand Y
% $U_{rel}(y)$	percent relative expanded uncertainty of the measured value y of measurand Y
$u_r(y)$	u of mean value of replicate measurements of Y performed under repeatability(r) conditions
$U(y)$	expanded uncertainty of the measured value y of measurand Y
$u(y)$	standard uncertainty of a measured value, y, of measurand Y
$\bar{x}$	mean value

5 Measurement uncertainty for medical laboratories

5.1 Measurement uncertainty concept

All measurement results include some error. Because of measurement imprecision, the magnitude of error in an individual result cannot be exactly known. The measurement uncertainty (MU) concept

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

recognises that a single measurement result is the best available value for a measurand and that other values are possible if the measurement were to be repeated on the same sample.

Based on the known analytical performance of the measurement procedure used, a measurement result of x units can be stated as having an uncertainty of u units.

This can be expressed as an interval of possible values for a measurand (see 5.4), with the interval defined as $x \pm u$ units. The value of the measurand is assumed by the laboratory to lie within the interval $x - u$ to $x + u$ units, with a stated level of confidence.

Medical laboratory measurement procedures are well-suited to utilizing internal quality control (IQC) and other available data to estimate MU without the need for measurement models and complex statistics. The following sections describe a practical method for medical laboratories to estimate u for their measurement procedures that utilizes available IQC data in addition to uncertainty associated with the assigned value of calibrators and the uncertainty of any bias corrections introduced.

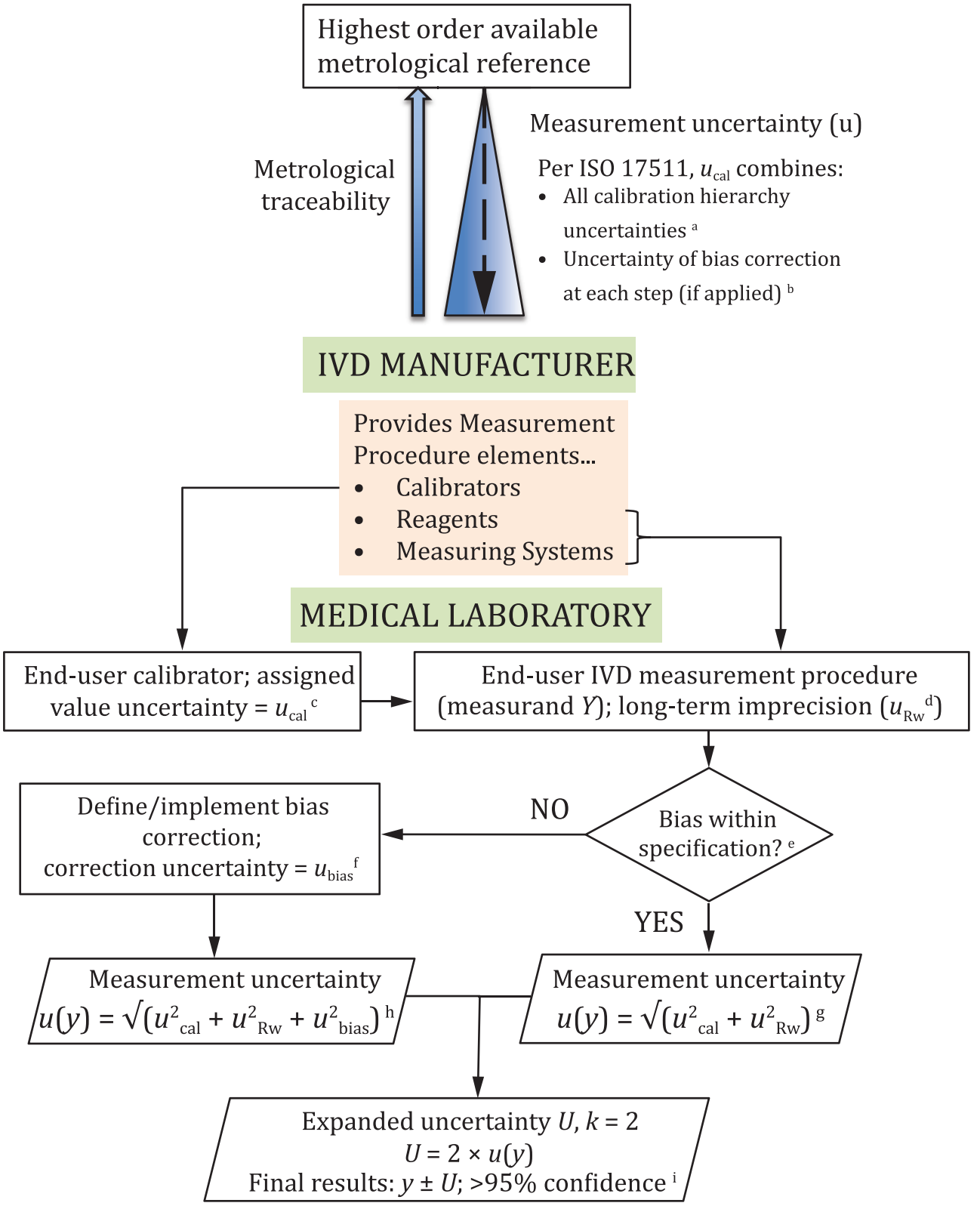
Figure 1 is a flow chart that illustrates the overall process to be followed by a medical laboratory in estimation of MU, and identifies the inter-relationships among major sources of MU that should be accounted for by the laboratory when estimating MU for a given measuring system.

MU only considers uncertainties arising from sources within the technical bounds of a measuring system and assumes that:

— uncertainties due to pre- and post-analytical steps are minimised by standardising these processes;

— measured human samples are typical and do not have unusual sample-specific factors (e.g. interferences) affecting measurement procedures.

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019



© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

[a] *Calibration hierarchy uncertainties*: Depending on the measurand, there can be multiple value assignment steps and associated uncertainties from the end-user calibrator back to the highest available reference. See ISO 17511.

[b] *Uncertainty of calibrator bias correction*: Note that an end-user calibrator manufacturing process already includes correction of any medically significant measurement bias relative to the highest order reference used, and therefore estimation of a bias by the end-user laboratory and subsequent estimation of a u_{bias} is rarely required. If further bias correction is required by the end-user medical laboratory, then the uncertainty of the bias correction, $u_{\text{bias,}}$ needs to be combined with the manufacturer's estimate of u_{cal} prior to calculating $u(y)$. See 6.6, C.6 and NOTES 5, 6 and 8.

[c] *Uncertainty of the value assigned to an end-user calibrator*: Calibrator manufacturers need to provide their estimates of u_{cal} to end-users on request.

[d] *Calculation of long-term imprecision, u_{Rw}*: Short-term estimates of the imprecision of a measuring system can underestimate u because required information can be lacking. Long-term imprecision estimates from IQC data collected across important changes to measuring conditions is usually more complete. The time required to collect sufficient data is mainly governed by measuring system specific factors such as measurement frequency, calibration frequency, frequency of reagent and calibrator lot changes, shelf-life of consumables, variable environmental conditions, among others., equipment maintenance procedures. See 5.3.

[e] *Measurement bias verification*: The laboratory needs to ensure that the magnitude of any measurement bias does not exceed the acceptable specification for medical use. External quality assessment (EQA) performance is often used for this purpose, but caution needs to be exercised. In addition to accounting for the commutability of the EQA material, the EQA target value can itself be biased, depending on how the value is assigned to the material. Where there are doubts concerning validity of a bias observed for an EQA material, the laboratory needs to consider assessing bias with human samples.

[f] *Bias correction*: Appearance of a medically unacceptable measurement bias can be detected by EQA surveillance providing that the EQA schemes fulfil some mandatory requirements, as described[20] [21]. If unresolved by the manufacturer, the laboratory can introduce a correction factor. If so, the uncertainty of the correction factor, u_{bias}, needs to be estimated and included in the calculation of $u(y)$. Use of bias correction factors are not permitted by some national regulations.

[g] *Calculation of MU of a final result, u(y); bias within specification:* This calculation takes into account the uncertainty of the value assigned to the calibrator, $u_{\text{cal,}}$ and long-term precision, u_{Rw}.

[h] *Calculation of MU of a final result, u(y); bias exceeds specification:* This calculation takes into account the uncertainty of the value assigned to the calibrator, $u_{\text{cal,}}$ long-term precision, u_{Rw}, and the uncertainty of any bias corrections, u_{bias}, introduced by the end-user medical laboratory.

[i] *Human sample results*: It is usual practice to expand u by multiplying it by a coverage factor (k) of 2 to provide an expanded uncertainty, U, with a level of confidence of approximately 95 % when associated with human sample results. Uncertainties are not required to be routinely reported to medical practitioners with results, but should be available on request. See 5.4.6.

Figure 1 — Process for estimation of measurement uncertainty for a typical in vitro diagnostics measuring system

5.2 Maximum allowable measurement uncertainty

The magnitude of MU should be suitable for a result to be used in a medical decision and ideally as small as technically possible. For a given measuring system, estimating the expanded uncertainty of the results produced is of very limited value unless it can be compared with an upper limit of allowable expanded uncertainty based on the quality of results required for medical use.

© ISO 2019 – All rights reserved
Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019

Such limits should be based on models defined by the 2014 European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) consensus conference[22] including clinical outcome studies, a selected proportion of biological variation, or, when information derived from the first two models are lacking, state-of-the-art of the measurement performance. The chosen approach is guided by factors such as the biological behaviour of the measurand, medical applications of results, and analytical performance characteristics of available measurement procedures. If a measurement procedure exceeds the upper allowable uncertainty limit, it may be possible to reduce the uncertainty by identifying and modifying a technical step that makes a relatively large contribution to the total uncertainty of results. If the uncertainty cannot be sufficiently reduced, a decision must be made as to whether the measurement procedure is to be changed or if the quality goal should be reconsidered.

The value selected by a laboratory for the maximum allowable MU and its justification forms part of the MU record for the measurement procedure.

5.3 Sources of measurement uncertainty

For each measurement procedure, it is important to identify the technical point from which uncertainty is to be estimated. Generally, this will be the point at which IQC materials enter the measurement process. If a procedure requires a pre-measurement sample preparation step and IQC materials also undergo this step, the laboratory must demonstrate that human samples and IQC material behave similarly. If IQC material does not undergo such a step, or is subjected to the pre-measurement sample preparation step, but behaves differently from human samples, the laboratory should design a study to estimate a typical uncertainty associated with the sample preparation process and combine it with the uncertainty of the measurement step.

Sources of uncertainty may arise from interfering substances that modify the interaction of the analyte with the measuring system and/or the signal generated by the measurement process. Examples include patient antibodies to an analyte or reagent, spectrophotometric interference by free haemoglobin, or cross-reactivity of structurally related molecules. These pre-measurement sources of uncertainty are generally individual sample-specific and not included in the estimation of MU for typical human samples.

Common sources of MU are:

— sample inhomogeneity;

— reconstitution procedures for lyophilised materials, e.g. calibrator and reagents;

— uncertainty of calibrator values, re-calibrations;

— instrumentation, e.g. electro-mechanical fluctuations, maintenance, parts replacement;

— reagent and calibrator instability;

— reagent and calibrator lot-to-lot variability;

— fluctuations in laboratory environment;

— operator bias introduced by reading analogue instrument indications;

— variable manual dexterity for manual and semi-automated methods;

— measurement bias vs. an accepted calibration hierarchy scheme;

— measurement formulae, e.g. approximations, assumptions, inexact values for constants, rounding of digits;

— more than one of the same measuring system for the same measurand;

— more than one measurement procedure for the same measurand that may have different analytical performance characteristics.

© ISO 2019 – All rights reserved

Documents
Document Sharing Hub
Full document details: PD ISO/TS 20914:2019