‘Measurement verification in the clinical laboratory:

A guide to assessing analytical performance during the acceptance testing of methods (quantitative examination procedures) and/or analysers’

David Burnett

Introduction

Medical laboratories in the UK seeking to be accredited to the ‘Standards for the Medical Laboratory’ published by CPA(UK)Ltd[1] or to the International Standard, ISO 15189:2007 Medical laboratories-Particular requirements for quality and competence, have to comply to particular requirements for examination procedures. This guidance to laboratories on measurement verification i.e the verification of quantitative examination[2] procedures (abbreviated to examination procedures from herein) prior to their introduction into routine use is to be welcomed for its simplicity and for the provision (courtesy of Anders Kallner) of practical statistical tools.

The title of the guidance indicates that it concerns ‘verification’ and not ’validation’ although in many publications the terms are often used interchangeably. This is understandable as in common English usage they are both defined as involving the provision of confirmatory evidence. ISO 9000:2005[3] provides definitions of both terms indicating that they should be used in a specific way in the context of ISO quality documentation. It has taken the author a long time to understand the differences in technical usage. To resolve this difficulty I have found that it is easier to use the ‘definitions’ rather than the ‘terms’ when describing their part in the steps from the **development of examination procedures** through to their **procurement and evaluation** prior to their use in the medical laboratory.

Development of examination procedures

The vast majority of examination procedures used in the medical laboratory originate from *in-vitro* diagnostic (IVD) manufacturers and are used without modification; only a minority being methods developed ‘in-house’ or manufacturer’s methods modified by the user. ISO 15189 stipulates that, irrespective of who develops or modifies such procedures, it shall be shown that they ‘…are suitable for intended use’ (clause 5.5.2) and CPA Standard F 1.1 requires that ‘Examination procedures, including those for sampling, shall meet the needs and requirements of users and shall be validated by the manufacturer/method developer for their

intended use'. In other words there should be '*confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled'*[4] . This implies that the intended use is understood and that the requirements (performance specifications) needed to fulfil that purpose can be defined. In practice the IVD manufacturer's aim will be to be 'to make systems of measurement having metrological characteristics better than those currently in the market'[5] and it is left to the medical laboratory to their specify requirements (performance specifications)' during the procurement process. There is an obligation, for example in European legislation,[6] that IVDs 'be designed and manufactured in such a way that 'when used under the conditions and for purposes intended, they will not compromise, directly or indirectly, the clinical condition or safety of the patients, the safety or health of users or, where applicable, other persons, or the safety of property…'. The Directive goes on to require that the devices, 'taking into account the generally acknowledged state of the art'…. 'must achieve the performances, in particular, where appropriate in terms of analytical sensitivity, diagnostic sensitivity, analytical specificity, diagnostic specificity, accuracy, repeatability, reproducibility, including control of known relevant interference, and limits of detection, stated by the manufacturer'. This seems to indicate that the manufacturer's goal should be to aspire 'to fulfil the intended purpose of the examination procedure'; tempered by the generally accepted state of the art. Evidence regarding these goals is represented by the 'performance characteristics' of the examination procedure set out in 'performances claims'.

Procurement and evaluation of examination procedures

ISO 15189 requires that the 'methods and procedures selected for use shall be evaluated and found to give satisfactory results before being used…' (clause 5.5.3) and CPA Standard F 1.2 requires that the 'Manufacturer/method developer's performance claims shall be verified prior to introduction and records kept of the methods used and results obtained '. In other words there should be '*confirmation, through the provision of objective evidence, that specified requirements have been fulfilled'*[7]. It follows that, as part of procurement, the potential user specifies their requirements (performance specifications) and that the evaluation process involves confirming that the manufacturer's performance claims (performance characteristics) meet the users specified requirements (performance specifications).

It important to understand that the confirmatory evidence required in the developmental stage is more extensive[6] than that in the procurement and evaluation stage. The development stage requires evidence '*…that the requirements for a specific intended use or application have been fulfilled,'* whereas the procurement and evaluation stage only requires '*…that specified requirements have been fulfilled'* and is generally restricted to; comparison of methods experiments to establish inaccuracy or bias, replication experiments to establish imprecision and a linearity check to determine the reportable range and sometimes collecting reference values to verify the reference range. It is a practical approach to these activities that is described in **'Verification of measurement procedures in the clinical laboratory'.**

[1] www.cpa-uk.co.uk CPA(UK)Ltd 'Standards for the Medical Laboratory' v 2.01 Mar 2009

[2] **A3.44 quantitative examination** <laboratory medicine> 'set of operations in which the amount or concentration of an analyte is measured and expressed as a numerical quantity value in appropriate measurement units' (ISO/FDIS 18113-1:2008)

[3] ISO 9000:2005 Quality management systems-Fundamentals and vocabulary

[4] The text in 'italics' is the ISO 9000:2005, clause 3.8.5 definition for 'validation'.

[5] Fuentes-Arderiu, X What is relevant in clinical laboratory sciences, goals or requirements? Accred Qual Assur (2005) 10:257-258

[6] Directive 98/79/EC on in vitro diagnostic medical devices. Annex 1 Essential requirements. (27 October 1998)

[7] The text in 'italics' is the ISO 9000:2005, clause 3.8.4 definition for 'verification'. The definition used in **''A guide to measurement verification in the clinical laboratory'** is from the International vocabulary of metrology (VIM) JCGM 200:2008. To all intents and purposes the two definitions have the same meaning.

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