



Letter to the Editor

Biological reference intervals and ISO 15189

The standard ISO 15189:2003 specifies particular requirements for the quality and competence of medical laboratories, and provides guidance for laboratory procedures to ensure quality and competence in clinical laboratory examinations [1]. An authorised accreditation body can accredit any clinical laboratory fulfilling the requirements given in this standard.

However, although this standard is specific for clinical laboratories, not all requirements are easily understandable. This type of requirements deserves special attention and clarification.

The subclause 5.5.5 states “Biological reference intervals shall be periodically reviewed. If the laboratory has reason to believe that a particular interval is no longer appropriate for the reference population, then an investigation shall be undertaken, followed, if necessary, by corrective action. A review of biological reference intervals shall also take place when the laboratory changes an examination procedure or pre-examination procedure, if appropriate.”

According to this requirement clinical laboratories seeking accreditation for compliance with ISO 15189:2003 shall demonstrate that the biological reference interval communicated to all users of laboratory services are appropriate for the reference population and for the patient population served, and for their measurement systems, of course. And this demonstration shall be done periodically.

The requirement of appropriateness may be fulfilled in different degrees. The options to fulfil this requirement depend on the origin of the biological reference intervals, the transferability of these values and the metrological and pre-metrological information available. Thus, these options, in decreasing order of appropriateness (from optimal to minimal), for a given biological quantity are the following:

1. *Production* of biological reference values and estimation of the biological reference interval by the clinical laboratory seeking accreditation, according to the IFCC recommendations [2].
2. *Simultaneous production* of biological reference values by the laboratory seeking accreditation and other clinical laboratories using the same measurement system in the same geographic area according to an appropriate

multicentre design, and estimation of the common biological reference interval from the blend of biological reference values from all laboratories [3,4] according to the IFCC recommendations [2].

3. *Adoption, after validation*, of a published biological reference interval estimated by other clinical laboratory—or by several clinical laboratories using different measurement systems according to an appropriate multicentre design [5–8]—according to the IFCC recommendations [2].
4. *Adoption, without validation*, of a biological reference interval published by other clinical laboratory, provided that the biological characteristics of both populations and the metrological characteristics of both measurement procedures are approximately the same.

Additionally, a “subminimal” option may be considered:

- *Adoption, without validation*, of a biological reference interval given in a publication without neither description of the reference population nor the metrological quality. [Note that this it is often done when adopting a biological reference interval given in a package insert or a textbook.]

This “subminimal” option might be accepted transitorily during the first period of accreditation, for example.

Regarding the validation of the adopted reference intervals, it may be done by measuring 20 samples from 20 reference individuals: (i) if 2 or fewer results are outside the proposed reference interval, this interval may be adopted; (ii) if 2 or more results are outside the proposed reference interval, measure another 20 samples from 20 reference individuals; (iii) if 2 or fewer results are outside the proposed reference interval, this interval may be adopted, on the contrary, the proposed interval must be disregarded [9,10]. Recently, a simple software to verify reference limits also using 20 reference individuals has been published [11].

With regards to the frequency whereupon the intervals must be reviewed, any recommendation does not exist, I think this review may be done once per year, during the management review process. Then, it may be decided—likely by professional judgement—if changes observed in day-to-day imprecision or in systematic error deserve the re-validation of a particular reference interval.

References

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