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EDMA Position Paper

Laboratory Medicine and Traceability
Views and needs of the industry for compliance with the essential requirements of the IVDD

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Background

Laboratory testing plays a major role in the diagnosis and monitoring of progression or remission of diseases. It also helps to identify persons at a higher risk level for certain diseases. In the interest of physicians, patients and society as a whole, consistency of results is a very important aim. Results always need to be seen in the medical context by the physicians who interpret the data of the individual patient.

The IVD-Directive (Directive 98/79/EC) requires manufacturers to ensure traceability of the values assigned to calibrators and trueness control materials* to reference measurement procedures and/or reference materials of a higher order, where available. This is a legal requirement for all CE marked products marketed in Europe but manufacturers are also interested in applying the principle of traceability on a global scale because this allows products to be marketed worldwide. The benefit to patients and users is perceived as the direct comparability of laboratory measurement results over regions and time.

For the concept to be applied in its complete form, ideally up to the highest possible level of metrological order, the unequivocal description of the analyte to be measured and of the detailed measurement procedures in human samples are necessary. The availability of a suitable reference material is also necessary. The assignment of the values must be performed by laboratories with the appropriate qualifications (accreditation), very often by laboratories of metrological institutions or other specially qualified laboratories.

However, while in clinical laboratories some 1000-1500 medically relevant measurands are presently determined, only for about 60 of them can the calibration be made traceable to the highest metrological order, e.g. glucose, cholesterol.

JCTLM (Joint Committee on Traceability in Laboratory Medicine)

Manufacturers are interested in the assessment of presently available reference preparations from various sources and of described reference measurement procedures. They support further development of reference materials and reference measurement procedures suited for the application in human serum and other fluids used for medical purposes. Therefore industry appreciates the efforts started by JCTLM with the support of IFCC and BIPM, to collect information on reference materials and methods and on existing experienced qualified reference laboratories, as well as to propose future suitable reference materials and measurement procedures.

In view of the limited resources and large efforts connected with these activities, clear priorities need to be set up. Projects need to take into account the clinical importance of the analyte and the technical difficulties which have to be overcome, and whether improvement of the metrological as-

* When talking about traceability all along this text, “control materials” mean always “trueness control materials”.

pects is reflected in a significant gain of medically relevant information.

WHO

WHO provides international standards, which are biological reference materials used to calibrate therapeutic or prophylactic (e.g. vaccines) products. They are also used for calibration of in-vitro diagnostic immunoprocedures. In contrast to the situation of clearly described chemical entities, the situation is more complex in these instances. In many cases the preparations are heterogeneous and are mixtures of several components (or isoforms), which are recognized differently by different monoclonal antibodies used in the immunoprocedures. At the same time, for their application as calibrator in laboratory medicine the species of interest in the biological fluid depends on the medical application. Ferritin species for the determination of anaemia, for example, are different from those for monitoring tumours, therefore the intended medical application must be kept in mind, when considering traceability.

WHO International Standards are widely used by manufacturers as calibrators of higher order; however these materials show some shortcomings and do not necessarily guarantee that patient results obtained with kits from different manufacturers are comparable, even when their calibration is traced back to the same material.

Laboratory medicine and industry would benefit from international conventional reference measurement procedures used with the appropriate international conventional reference materials, which serve as surrogate material for the “analytes” existing in human samples.

In order to make progress for reference materials for in-vitro diagnostic applications, reproducibility and consistency of the materials over time is needed, which involves:

- Description of the source of material (samples of patients with defined clinical stages or surrogate material)
- Validated procedure for processing and aliquoting the material
- Stability assessment
- Description and assessment of the procedure(s) used to assign target (consensus) values by the laboratories participating in the interlaboratory studies.
- Description of the experimental model to obtain the consensus value, including the statistical evaluation protocol and an indication of uncertainty
- Consistency of lot-to-lot results.

CONCLUSIONS

IVD-industry sees the international scientific organizations in laboratory medicine covering the leading role: they are in the best situation to provide the scientific basis and to assess the required quality of results in view of the medical needs. Industry provides most of the reagents, instruments, calibrators and control materials, which are used for routine analysis. The support of international metrology institutions and WHO is required to provide material and methods on a sound basis to achieve consensus on a global level.

Compliance with the essential requirements of the IVD directive

As part of the general essential requirements laid down in Annex IA section 3 is the requirement that:

“The traceability of values assigned to calibrators and/or control materials must be assured through available reference measurements procedures and/or available reference materials of a higher order.”

Compliance with this particular requirement raises the following issues:

Information supplied by the manufacturer

What information needs to be provided by the manufacturer concerning metrological traceability?

This is an important question as it is likely that information pertaining to traceability will be requested by customers, competent authorities and possibly even third parties. Manufacturers are only a part of the chain that ensures traceability to the controls and calibrators, which also includes international metrological organizations and sometimes national metrological institutes which define and prepare standards of higher order.

Thus, the manufacturer should comply with the requirement of the directive and its supporting documents, e.g. EN ISO 17511, by providing the user with information pertaining to the reference material to which the calibrators and/or trueness controls are traced.

The uncertainty of measurement (UoM) associated with the values of the calibrators and/or controls provided by a manufacturer, should be calculated according to the guidance in EN ISO 17511. Whether, at this stage this value should be disseminated is still unresolved. Guidelines for clinical laboratories explaining to whom, under what conditions and to what extent the UoM of calibrators and test results have to be given are going to be prepared at the level of the CLSI and ISO/TC 212.

Upon request by competent authorities the manufacturer may provide further information but it should be noted that it is unlikely that the manufacturer has all the information pertaining to the control and calibration steps which take place outside of the manufacturers control, be it in metrological institutes which set up primary and secondary reference procedures and calibrators, or at the level of the end user who may have his own reference procedures. Thus the full disclosure of transfer protocols does not provide per se useful information.

Any third parties interested in the traceability chain would be provided with the information addressed to the user.

Changing reference materials

A second issue which arises is how to go about the implementation of a change in calibrators when a new higher order reference material becomes available, for instance by publication by the JCTLM in one of the available lists.

To ensure the safety of medical diagnostics results, manufacturers cannot be expected to change calibrators overnight. Not only does a change in calibrator entail a significant amount of tests and controls to establish a new chain of traceability, but in the case where the change in calibrator would result in a significant change in the values of the assays, due care must be taken to inform clinicians of this change and to minimize the risks associated with it. Although specific cases will be faster than others, this whole process requires proper coordination and cannot be expected to be completed in less than a year, though in particularly complex or high risk situations the process may take even longer.

However in spite of the time required manufacturers should endeavour to adopt the higher order reference material as soon as is feasibly possible so as to remain in compliance with the IVD directive.

EDMA Standardisation Quality and Risk Management Working Party