National Measurement System

In the balance – measurements for improving therapeutic drug monitoring

LGC is developing a range of certified reference materials to help IVDD compliance and the setting of tighter threshold levels for therapeutic dosing.

LGC *Setting standards in analytical science*

The Requirement

Therapeutic drug monitoring (TDM) is a means of controlling and individualising a patient's drug therapy by monitoring and adjusting drug concentrations in the body. This enables clinicians to ensure an optimum balance between therapeutic effect and adverse side-effects. TDM ensures that the concentrations of drugs given to a patient are sufficient to, for example, prevent a patient from rejecting their new organ, keep AIDS at bay in HIV positive patients, and minimise the risk of seizure in epileptic individuals. TDM therefore plays a vital role in helping individuals with chronic conditions to live normal lives.

As such drugs have a narrow therapeutic range, an optimum balance between therapeutic effect and the occurrence of adverse events needs to be ensured. Therefore, accurate measurement has a direct impact on clinical intervention. However, whilst individual hospitals meet local quality standards, it does not necessarily mean that measurement results are comparable between hospitals.

The In Vitro Diagnostic Medical Devices Directive (EC IVDD, 98/79/EC) stipulates 'the traceability of values assigned to calibrators and/or control materials must be assured through available reference measurement procedures and/or available reference materials of a higher order'. This ensures harmonisation of standards across Europe, providing a high level of health protection for patients. It is therefore necessary that high accuracy, low uncertainty, reference materials are available to satisfy the objectives of the Directive. At present, the number of IVD devices and potential measurands vastly exceeds the number of higher order reference materials available.

The Solution

LGC is helping to address this problem by developing a range of certified reference materials to ensure measurements by TDM are accurate and traceable to the SI through a higher order reference material. This will help IVDD compliance and the setting of tighter threshold levels for therapeutic dosage.

Digoxin, a drug used in the treatment of congestive heart failure and cardiac arrhythmia has a narrow therapeutic range. A scene in the film Casino Royale where James Bond tries to defibrillate himself after being poisoned by a Vesper Martini tainted with digoxin, highlights, in true Hollywood style, the toxic effects of digoxin.

LGC's two digoxin reference materials closely match the upper and lower levels for digoxin monitoring. Both are certified as European Reference Materials (ERM®) and made under LGC's accreditation to ISO Guide 34 for the production of reference materials. They are intended for use by clinical laboratories to determine digoxin levels in human serum through method validation and performance monitoring of methods, providing an effective means of measurement traceability.

LGC is also developing a matrix certified reference material for tacrolimus, an immunosuppressant drug used in transplant surgery, in whole blood. Levels of tacrolimus in a patient's blood are measured by liquid chromatography mass spectrometry (LC-MS) and immunoassay based methods, which are all calibrated independently, without agreement on a common reference point such as an accepted reference method or higher order tacrolimus reference material. This means that mass concentration values may not be comparable between methods or laboratories and, in severe cases, this can lead to the patient either receiving an insufficient dosage of tacrolimus and possibly rejecting the organ, or receiving a high, potentially toxic dose. LGC's reference material will improve confidence in measurement, irrespective of the analytical platform used, and will enable clinicians to set and maintain optimal patient dosage for the benefit of their patients and the wider healthcare system.

Impact

Gill Holcombe, Head of Reference Material Production at LGC explains:

> *"LGC's new reference materials will improve confidence in measurement, helping clinicians to ensure optimal therapeutic effect and minimise the occurrence of adverse events."*

These new reference materials join a digoxin reference material certified for purity, which is already available commercially. This pure material is intended for use primarily as a calibrant in methods of analysis for digoxin in serum.

LGC is now using this expertise to develop more reference materials for drugs used in TDM. The latest of which is for sirolimus, another immunospressant drug, where both pure and matrix reference materials are under development.

Reference materials are commercially available through LGC Standards, a division of LGC that is a dedicated supplier of reference materials and standards to a wide range of industrial sectors.

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