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Basics and Traceability of Certified Reference Materials

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Key to the establishment of a Certified Reference Material is the definition and establishment of the 'traceability' of the values given to accepted national or international standards through an unbroken chain of comparisons all having stated uncertainties expressed as a correct (sub)multiple of the relevant SI unit or another internationally agreed measurement scale.
The certification to SI is done by metrological preparation, use of primary measurement methods in a 'reference laboratory', and by laboratory intercomparison. Rules for this process and examples were given in the lecture.
Certification is, however, more than a series of precise, accurate, and traceable measurements.

- Extreme care has to be taken not only to prepare a stable, homogeneous base material, but also to store the sample in a tight and inert containment.
- Matrix CRMs should be dry and clean, transformed into an optimal physical and chemical form, set at the correct temperature and water activity level from an early stage of the production process and packaged under argon in an absolutely tight container.
- Homogeneity has to be assured between the units of a batch and within the same bottle of the material. A statistical approach is given to establish homogeneity .
- Stability testing has to be performed under normal and stress temperature conditions, also stating the transport conditions, and has to be part of the production procedure. The time period for which the certified value of the CRM remains valid has to be guaranteed. The concept of 'isochronous measurements' was discussed and the uncertainty component of long-term stability established.

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Use and Establishment of European Pharmacopoeia Reference Substances

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Chemical reference substances and biological reference products of the Pharmacopoeia are employed as analytical reference standards for a number of purposes including the confirmation of identity, chromatographic performance tests, the content of impurities or for the determination of content of drug substances and dosage forms. These reference materials are an integral part of the monographs of the Pharmacopoeia which sets the legally binding standards for drug substances and products in the 26 European member states signatories to the 'Convention on the Elaboration of the European Pharmacopoeia' and further enforced by Directives of the European Union.
The different uses of the reference solutions were described.
The methods of establishment were discussed in relation to the different guidelines which have been published (*e.g.* ISO/REMCO, WHO, Ph. Eur.). Particular attention was given to the establishment of chemical reference substances employed as standards for selective assays. These reference substances are method specific and comparisons were drawn between reference materials (ISO) and reference substances (Ph. Eur.).
The issue of uncertainty of the assigned value and the supply of certificates were also discussed.

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Design, Production, and Characterization of Reference Materials

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A comprehensive overview on the work of NIST in establishing and certifying Standard Reference Materials was given.
A catalogue and further information can be ordered from the following address:
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Use of Reference Materials in Analytical Measurement

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The concept of the reference material as the carrier of the traceable value was established.
The result (the amount of substance in the investigated material) is a number with a unit and an uncertainty. It is derived from a measurement procedure based on a reference material that is the carrier of a value traceable to a primary measurement in the SI system.
The components of the uncertainties that arise from the different steps of the procedure were shown:
- primary reference material
- reference solution
- sample solution
- sample of the material
- material.

On the example of the determination of iopamidol by HPLC (USP), the contribution of the influence quantities of the steps of the procedure to the combined standard uncertainty of the final value was discussed and a 'Cause and Effect Diagram' for all steps was established. This example and evaluations of procedures for the determination of Pb, BHT, C18:1 (ester) and the Iodine Number taken from the 'IUPAC – Standard Methods for the Analysis of Oils, Fats and Derivatives' show that the combined uncertainties are generally underestimated.
Finally, a guideline of how to handle recoveries of the analyte in a given procedure was given.

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- 'Software System for Quantifying Uncertainty in Analytical Measurement (MUSAC)', under development: *http://www.empa.ch/metrology*

Establishing a National Reference Laboratory for Analytical Chemistry

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Based on a general traceability chain for the results of chemical-analytic measurements, the organization and the task of a national reference laboratory was presented based on the example of Switzerland. Traceability to the SI is achieved by a 'primary measurement' or in other words, by the 'experimental realization of the definition of SI units' which partly requires primary reference materials. A clear understanding of the role of reference materials in traceability of measurement results is often lacking. Therefore a distinction must be made between different types of reference materials with respect to their role.
The reference material used for calibration is introduced as the transfer standard for the traceable value whenever its value has been verified by a primary measurement, *e.g.* in a certification process. The main primary methods which are applied at EMPA were presented briefly. The main focus, however, was on the primary reference material. The basic concept of producing and using a primary reference material was shown in a current example from element analysis. However, it can be translated accordingly to any other analytical field.
Element analysis by means of spectrometric techniques which are widely used is based on element standard solutions which are used for calibration. These solutions are produced from pure elements or compounds. However, they are not traceable to the SI in most cases. A serious certification study requires highly pure elements or compounds, *e.g.* primary material. However, only a few fully characterized materials with sufficiently high purity and low uncertainty are available commercially. Therefore, they have to be provided by the metrological institution itself. Many institutes purchase a large stock of material and put a lot of effort into its full characterization including all impurities. A fundamental problem of this approach is the fact that the 'stock of primary material' will be used up after a certain period of time and thus, the primary standard is irretrievably lost. With regard to pure metals for example, there is another problem as the determination of non-metallic impurities such as oxygen, nitrogen, carbon and others with sufficient precision is difficult and very time consuming. To avoid these problems, EMPA has chosen an alternative approach. A most elegant solution would be to simply eliminate these impurities in a reproducible process within a given uncertainty range to attain the desired purity. If sufficient reproducibility of this purification process can be proven, two major advantages are achieved. First, the time-consuming analysis of all impurities can be avoided for each batch. Secondly, as the primary material can be produced in equal quality when required, the primary standard becomes independent of time and location. The concept of this approach and first results were shown for zinc.