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Certified Reference Materials – Fact, Fiction, or Fantasy

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Evolution of Quality Standards

The need for higher quality data – Certified Reference Materials (CRMs)

ISO 9001 ⟹ ISO Guide 34 ⟹ ISO/IEC 17025 ⟹ (ISO 17034)

However,
The ISO Standards are confusing,
generalized, and subject to interpretation

There are many different approaches

We have not yet achieved true standardization

This presentation will just scratch the surface – we will cover some of the main attributes of a proper CRM (and some things to look for)

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Certified Reference Material (CRM) - Defined

ISO Guide 35

Reference material, characterized by a metrologically valid procedure for one or more **specified properties**, accompanied by a **certificate** that provides the **value** of the specified property, its associated **uncertainty**, and a statement of metrological **traceability**

NOTE 1 The concept of value includes qualitative attributes such as identity or sequence. Uncertainties for such attributes may be expressed as probabilities. (remember this for later)

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Important Points

- CRMs are generally thought to be of the highest metrological status
- CRMs can be produced by National Metrological Institutes (NMIs) or by **accredited Reference Material Producers**
- Commercial organizations that are **doubly accredited** to:

ISO Guide 34 and **ISO/IEC 17025** may **legitimately claim**

to Produce and **Certify** → **CRMs**

(*according to ISO definitions and standards*)

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Environmental

There are many representations in the market space – some good, some not so good

There are companies that are not accredited and call their standards Certified Reference Materials (Fantasy)

There are Certificates ranging from simple (possibly Fiction) and incomplete to expansive and very complete (probably Fact)

Some organizations make it difficult to distinguish between Certified and non-certified Reference Materials – just because an organization is accredited doesn't mean the product is a CRM (hard to distinguish Fiction from Fact)

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There are some Rules

(if you are accredited to ISO/IEC 17025 and ISO Guide 34)

But No Laws

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Governing Documents

The CRM world is organized around:

NMI's

The ISO Guide Series 30-35

- Especially Guide 34

ISO/IEC 17025

- And ISO/IEC 17043 (Proficiency Testing)

Simple, Right

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Remember the Definition – the Certificate

ISO Guide 35

Reference material, characterized by a metrologically valid procedure for one or more specified properties, accompanied by a **certificate** that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability

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Certificate of Analysis - Ambiguity

ISO Guide 31

Contains, **at a minimum:**

- Name of the material
- Producer and producers code for the material
- General description of the material
- Intended use
- Instructions for proper use
- Instructions for appropriate conditions of storage
- Certified property value(s), each accompanied by a statement of uncertainty
- Method(s) used to obtain property values
- Period of validity, if appropriate
- **And a lot of "shoulds"**

In spite of this, there is no "standard" Certificate

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Remember the Definition - Traceability

ISO Guide 35

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Traceability

ISO Guide 30

Property of the result of a measurement of the value of the standard whereby it can be related, with a stated uncertainty, to stated references, usually national or international standards, **through an unbroken chain of comparisons.**

Note: Accrediting Bodies have
their own defined policies on traceability

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Multiple ways to achieve Traceability

- By traceability to SI units
  - Gravimetry: NIST traceable weights e.g., Kilogram
- By comparison to a CRM
  - Obtained from an NMI
  - Obtained from a doubly accredited producer
  - Can be through assay, calibration, system suitability, or a control sample
- Through the use of a Standard Method
  - Weak traceability, limited application
- By comparison to a physical constant (not common with chemical reference materials)

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Things you will see

No mention of traceability — Not so good

- May or may not be any, but why wouldn't you say so?

Calibrated with NIST traceable weights — Good

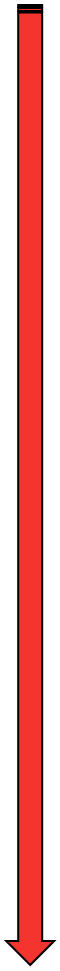
- Good but only part of the story

Traceable to a CRM — Better

- Very good **additional** traceability

Traceable to NIST standards (assay/calibration) — Best

- Common for elemental standards
- Less common for organics
- A high level of traceability



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Remember the Definition - Uncertainty

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Uncertainty - The most misunderstood term

Definition: The range of values within which the "True Value" may reasonably be expected to fall, at a stated level of confidence, usually 95%

- Uncertainty is not a measure of error
- It is a measure of the variability of a system
- Expressed as a **value ± another value** (of the same units)
- Uncertainty is an estimate
- Actually, it's a measure of Certainty!

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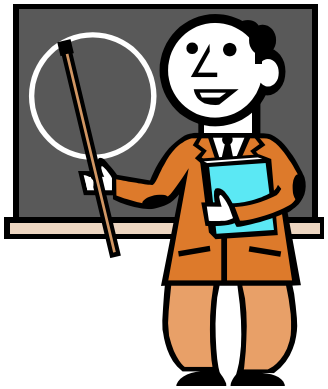
Uncertainty - Expectations

Statistician – Higher Uncertainty



Marketing – Lower Uncertainty

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There are only a few ways to achieve low uncertainties

- A very robust, precise method used to test a simple system: e.g., a single component neat material, tested by qNMR, calibrated with a NIST SRM

- Leave out sources of uncertainty

Assessors are suspicious of low uncertainties and you should be too

Less is not always better

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Components of Uncertainty for a CRM

- Characterization – u_{char}
- Homogeneity – u_{hom}
- Short Term Stability – u_{sts} (shipping conditions)
- Long Term Stability – u_{lts} (at indicated storage)

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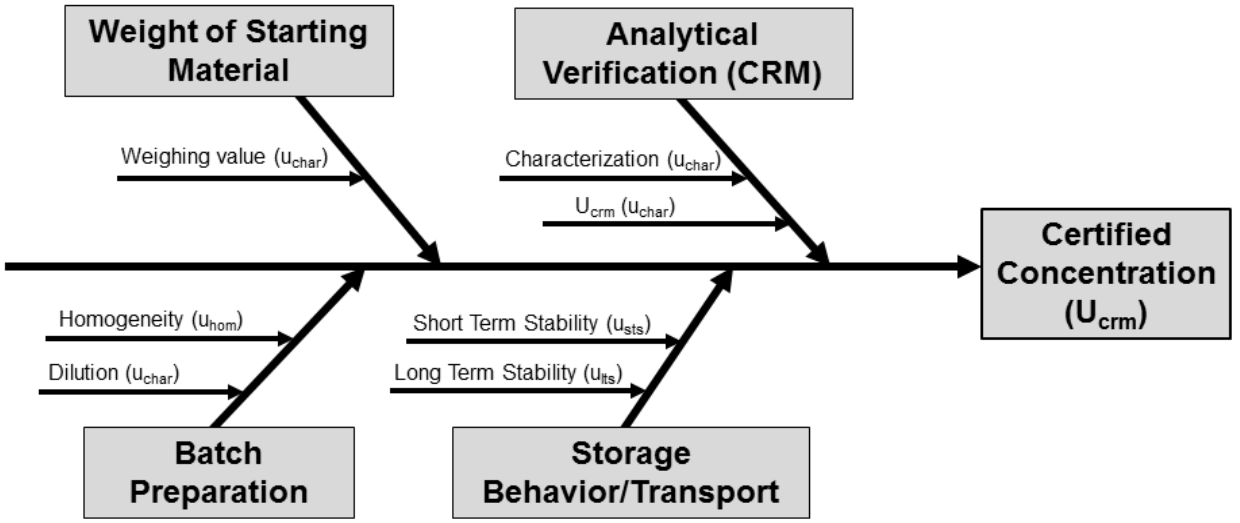
Fishbone diagram – method for capturing sources of Uncertainty



$$U_{crm} = k\sqrt{u_{char}^2 + u_{hom}^2 + u_{sts}^2 + u_{lts}^2}$$

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Uncertainty – the Math

$$u_{comb} = \sqrt{u_{char}^2 + u_{hom}^2 + u_{sts}^2 + u_{lts}^2}$$

(Addition in Quadrature)

Coverage factor, k from Student's t-distribution at the 95% confidence level (most just use 2)

$U_{crm} = u_{comb}k$, therefore:

$$U_{crm} = k\sqrt{u_{char}^2 + u_{hom}^2 + u_{sts}^2 + u_{lts}^2}$$

This is the formula for Expanded Uncertainty, no if, ands, or buts.

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So, here is where the problem comes from

ISO/IEC 17025:2005

5.4.6.2 Testing laboratories shall have and shall apply procedures for estimating uncertainty of measurement. (ok, so far so good) In certain cases the nature of the test method may preclude rigorous, metrologically and statistically valid, calculation of uncertainty of measurement. (hmm) In these cases the laboratory shall at least attempt to identify all the components of uncertainty and make a reasonable estimation, and shall ensure that the form of reporting of the result does not give a wrong impression of the uncertainty. (uh oh!) Reasonable estimation shall be based on knowledge of the performance of the method and on the measurement scope and shall make use of, for example, previous experience and validation data. (so, I can do whatever I want as long as it sounds reasonable?)

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This leads to all sorts of strange things

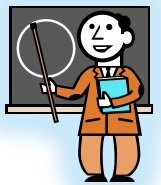
Things that you will see/hear:

Multiple uncertainty values

- $U_{crm} = k \sqrt{u_{char}^2 + u_{hom}^2 + u_{sts}^2 + u_{lts}^2}$
- There is only one uncertainty

Significant digits

- e.g., 100.5347 µg/mL ± 5.4728 µg/mL
- Implies a level of precision that is not possible



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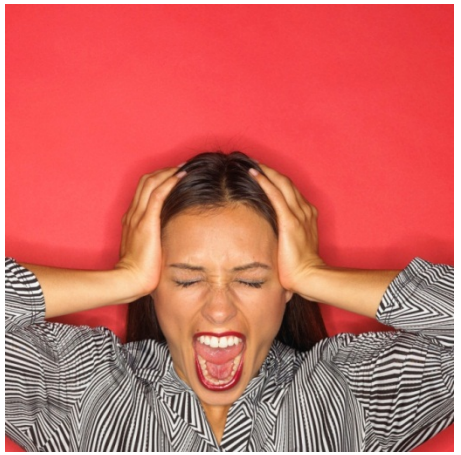
More things that you will see/hear



Uncertainty values that are all the same

- General estimates
- Reflects a poor understanding of statistics
- Implies no testing was done

Very small uncertainty

- All sources of uncertainty probably not considered

No uncertainty at all: N/A?

- Really, you can't make this up
- Remember the definition

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Environmental

Remember the Definition - Uncertainty

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Homogeneity

ISO Guide 30

Condition of being of uniform structure or composition with respect to one or more specified properties.

- A component of uncertainty

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Homogeneity – Production of a CRM

?

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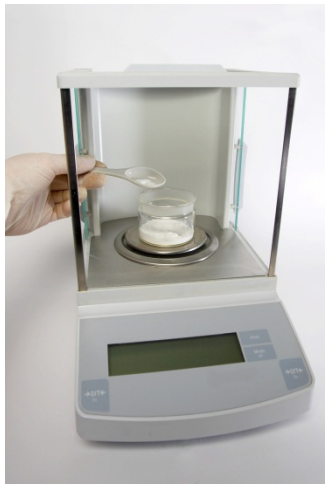
Homogeneous? How could it not be?

A typical solution CRM

Calibrate

Weigh



Dilute

Mix

Homogeneous? Yes, but….

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The Ampuling Process

Variables:

- Solvent
- Components
- Pumping
- Dispensing
- Headspace
- Inert gas purge
- Flame sealing
- Pyrolysis
- Time

Is it Homogeneous now? Maybe….

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So, how do we measure homogeneity?

Testing - We actually measure the uncertainty of our ability to detect heterogeneity

Typically: Random Stratified Sampling protocol

ISO Guide 35 recommends a minimum of 10 samples analyzed in triplicate

Data processed using ANOVA

The uncertainty of homogeneity must be included in the Uncertainty Statement

$$u_{comb} = \sqrt{u_{char}^2 + u_{hom}^2 + u_{sts}^2 + u_{lts}^2}$$

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Stability

Ability of a reference material, when stored under specified conditions, to maintain a stated property value within specified limits for a specified period of time.

ISO Guide 30

Editorial note: Stability is usually (and should be) an insignificant contribution to Expanded Uncertainty for properly designed CRMs

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Stability – the Dilemma

Two types of Stability: transport (sts) and storage (lts)

STS: Assessed by accelerated stability studies or actual transport and testing (very imprecise and impractical)

LTS: Assessed by periodic testing or extrapolation from accelerated conditions using the Arrhenius Equation

No standardized approach or set of specifications

- A standard that exhibits instability is not a very good CRM

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Conclusions – We've made progress!

Progress

Wild West
Reference Materials

Organized Chaos
Certified Reference Materials

But, we still need:

Consistent interpretation of standards
Clarification from Accrediting Bodies
Education of the user community

Caveat Emptor

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Thank you

Questions

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