CRM Second Source and Stability

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Topics

- **Second Source Lot Reference Material (RM)**
  - Purpose of Second Source
  - Options for Procuring a Second Source
  - Manufacturers of Starting Materials (MSMs)
- **CRM Stability**
- **Reasons for CRM Variations**

Second Source Lot RMs

Purposes of a Second Source Lot

1. Qualitative Agreement: Confirm Identity of Compounds in Primary Standard
2. Quantitative Agreement: Confirm Concentrations of Primary Standard Compounds
3. Degradation: Monitor and identify if occurring during analytical sequences

Second Source Lot RMs Options

1. Purchasing Two Lots from Reference Material Producers (RMPs)

	Purchase from Same RMP	Purchase from Different RMPs
Perceived Advantages & Disadvantages 	• Better quantitative agreement between lots • Lower cost & easier to purchase • Matching lots containing same compounds • Less assurance lots are significantly different	• Less quantitative agreement between lots • More expensive & difficult to purchase • Different lots may not match exactly • Greater assurance lots are significantly different

Second Source Lot RMs Options

2. Purchasing Two Lots Made from Different Starting Materials (SMs)

	Purchase From Same or Different RMPs
Perceived Assumptions 	• Better quality assurance since they are different starting materials • More representative of a true second source
Unperceived Disadvantages	• Increased probability of error • Hard to confirm between RMPs • More expensive • Second source not available

Requirements for Manufacturers of Starting Materials (MSMs)

ISO 17034:

…there are internationally recognized requirements and assessment processes for the evaluation of RMPs in which the competence to produce a RM is determined

Requirements for Manufacturers of Starting Materials (MSMs)

- **ISO 17034:**
  - There are no similar requirements for the MSMs (of chemicals, pesticides, etc.) from which the RMs are being produced that assess their competency to produce that starting material(SM)
  - MSMs are not typically in the business of producing a product with the intent of it being used as a SM for a RM

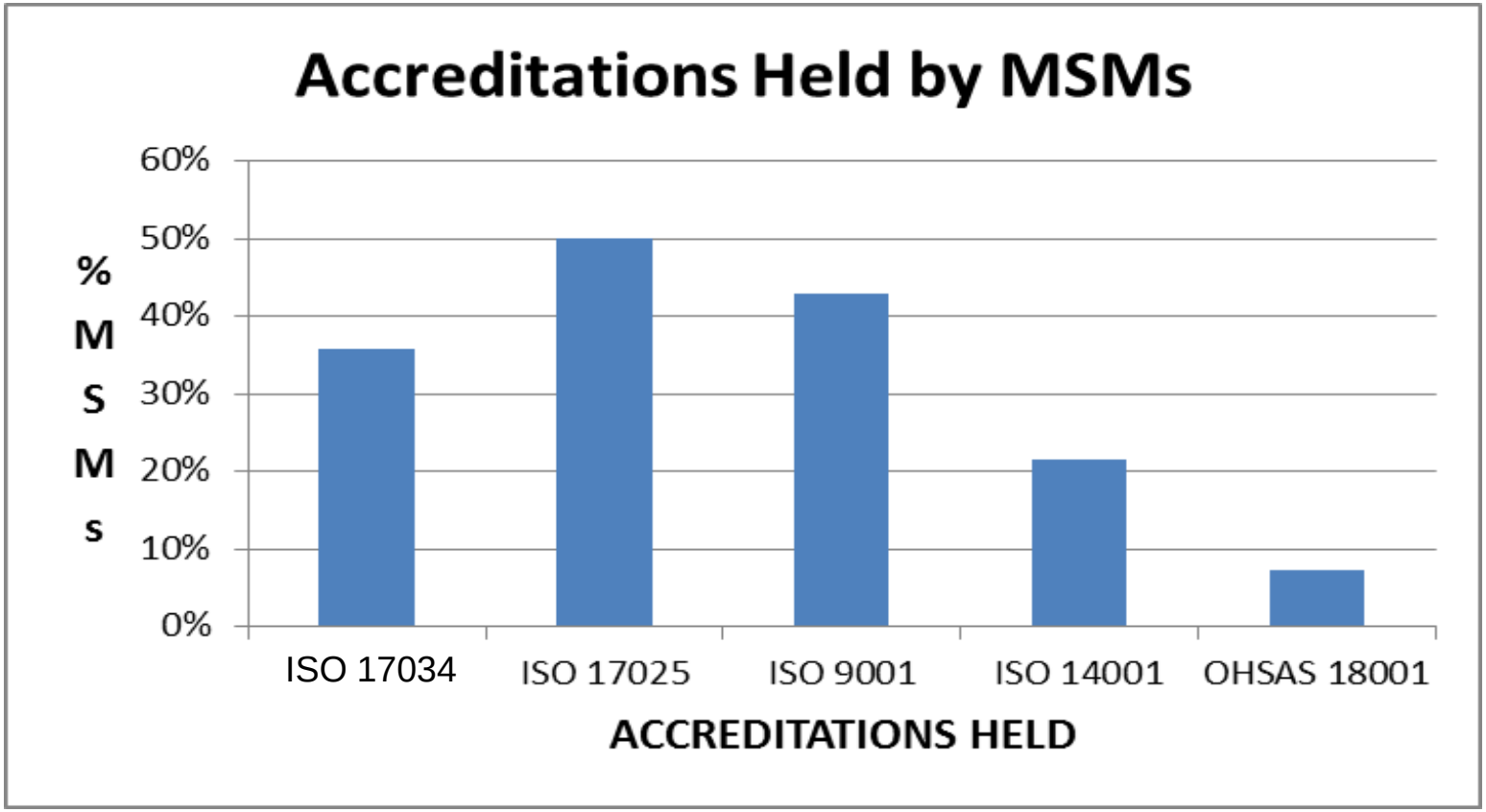
Requirements for Manufacturers of Starting Materials (MSMs)

- **ISO 17034:**
  - The responsibility for characterizing SMs ultimately lies with the laboratory and/or RMP

Accreditations of MSMs

Accred.	Covers	Addresses chemical identity and purity
ISO 9001	Quality Management Systems	No
ISO 17034	Competence of Reference Material Producers	Yes
ISO 17025	Competence of Laboratories	Yes
ISO 14001	Environmental Management Systems	No
OHSAS 18001	Occupational Safety and Health	No

Accreditations of MSMs



Note: 35% of 14 MSMs hold no accreditations that assess the competency to produce a SM

Starting Material Purity & Identity

Purity Notes on COA:

- **Purity and/ or chemical Identity** are determined by one or more techniques:
  GC/FID, HPLC, GC/µECD, GC/MS, LC/MS, RI and/or melting point
- Compounds w/purity < 99% have been weight corrected using a correction factor
- Purity of isomeric compounds is reported as the sum of isomers
- Purity values are rounded to nearest whole number

Second Source Lot Definition

ISO Guide 30(E) Definition of Lot:

- Lot - definite amount of material produced during a single manufacturing cycle, and intended to have uniform character and quality.

- Note: Does not require use of a different starting material source

CRM Stability

- Prior information
  - Use data from related materials
  - Use published and/or readily available information
- Stability studies
  - Accelerated testing
  - Long-term testing
  - Determines the value of the contribution to the combined uncertainty for instability
  - **Ensures stability in packaged container until opened**

CRM Stability Requirements

- Not reactive during normal use
- Retains properties
  - In expected timescale
  - In the presence of expected conditions of application
- Unstable materials Characterization
  - corrode, decompose, polymerize, burn or explode under the ‘normal’ conditions

CRM Certificate of Analysis

General Certified Reference Material Notes

Expiration Notes:

- Expiration date valid for unopened ampul stored in compliance with the recommended conditions.
- Uncertainty, concentration, and expiration of the CRM are based on the unopened product being stored according to the recommended condition found in the storage field.

Purity Notes:

- Purity and/or chemical identity are determined by one or more of the following techniques: GC/FID, HPLC, GC/µECD, GC/MS, LC/MS, RI, and/or melting point.
- Compounds with a listed purity of less than 99% have been weight corrected to compensate for impurities and/or salts. A correction factor is used to calculate the amount of compound necessary to achieve the desired concentration of the parent compound in solution.
- Purity of isomeric compounds is reported as the sum of the isomers.
- Purity values are rounded to the nearest whole number.

Certified Uncertainty Value Notes:

- The uncertainties are determined in accordance with ISO 17034 and Guide 35. The certified combined stressed uncertainty value (includes gravimetric uncertainty, homogeneity between-ampul uncertainty, storage stability uncertainty and shipping stability uncertainty and were combined using the following formula:

$$U_{combined\ stressed} = k\sqrt{U^2_{gravimetric} + U^2_{homogeneity} + U^2_{storage\ stability} + U^2_{shipping\ stability}}$$

k is a coverage factor of 2, which gives a level of confidence of approximately 95%.

- It is important to note that the shipping stability uncertainty was obtained under temperature extremes for specific time intervals; therefore, the certified combined stressed uncertainty value should only be applied to the product if it was stored at non-standard temperature conditions up to and including 7 days. Contact Restek Technical Service at www.restek.com/Contact-Us for use recommendations if your shipment was in-transit for more than 7 days at non-standard temperature conditions.
- Apply the certified combined unstressed uncertainty value if the product was received under standard shipping conditions. Apply the certified combined stressed uncertainty value if the product was received under non-standard conditions as specified below.

Label Conditions	Standard Conditions	Non-Standard Conditions
25°C Nominal (Room Temperature)	< 60°C	≥ 60°C up to 7 days
10°C or colder (Refrigerate)	< 40°C	≥ 40°C up to 7 days
0°C or colder (Freezer)	< 25°C	≥ 25°C up to 7 days

- Separate (not combined) uncertainty values for gravimetric uncertainty are also displayed on the certificate, if needed, separate homogeneity between-ampul uncertainty, storage stability uncertainty and shipping stability uncertainty values are available by contacting Restek Technical Service at www.restek.com/Contact-Us.
- The packaged amount is the minimum sample size for which uncertainty is valid. The ampules are over-filled to ensure that the minimum packaged amount can be sufficiently transferred.

CRM Certificate of Analysis

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Reasons for CRM Variations

- Re-setting %Purity of SM based on analytical determination of impurities
  - Final concentration based on revised purity vs. %purity value on SM label
- Wrong SM
  - Mislabeling Error
  - Handling Error
  - Non-Specific Analytical Identification
    - Melting point, FID

Reasons for CRM Variations

- Blunders
  - E.g., dilution error, forget to add, added twice
- Poor Technique or Wrong Procedure
  - Non-quantitative transfer (e.g., techniques for viscous liquids or gases)
  - Solubility (wrong solvent used)
- Instability – Breakdown due to reactivity
  - Storage container
  - Other compounds, or solvents in a mixture

Reasons for CRM Variations

- Expiration Date Policy
  - Date of manufacture vs. date of shipment
- SM Manufacture Variations

Reasons for CRM Variations

- Custom vs. Stock RMP Products
  - Are ***Custom*** CRMs tested to the same QA specifications as ***Stock*** CRMs?
  - Does the RMP's ISO Accreditation or Certification include their ***Custom*** RMs?
  - Varying Levels of Quality offered for Custom CRMs, or RMs
    - Level A – Gravimetric Only
    - Level B – Qualitative
    - Level C – Quantitative

Conclusions & Recommendations

- Application and Use of Second Source Materials
- Better Understanding of CRM Stability
- Understand Variations Among CRMs:
  - RMPs verification procedures for identity & % Purity of SMs
  - RMPs procedures for second source CRMs
  - RMPs Policy on setting expiration dates

Thank You for Your Kind Attention

Questions?

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