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Model for Uncertainty Evaluation : A Practical Approach in the Certification of CRM

Performing certification and homogeneity test simultaneously

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Introduction (1)

◆ Current Model for a batch characterization of CRM in ISO G 35

$$x_{\mathrm{CRM}} = x_{\mathrm{char}} + \delta x_{\mathrm{bb}} + \delta x_{\mathrm{sts}} + \delta x_{\mathrm{lts}} \qquad (1)$$

x_{CRM} denotes the property value;

x_{char} denotes the property value obtained from the characterization of the batch or, in the case of a single artefact characterization, the property value obtained for the artefact;

δx_{bb} denotes an error term due to the between – bottle variation;

δx_{sts} and δx_{lts} are error terms due to the short – term and long – term instability.

Usually, homogeneity and stability studies are designed in such a way that the values of these error terms are zero, but their uncertainties may not

◆Uncertainty relationship of CRM certification (ISO G 35)

$$u_{\mathrm{CRM}} = \sqrt{u_{\mathrm{char}}^2 + u_{\mathrm{bb}}^2 + u_{\mathrm{sts}}^2 + u_{\mathrm{lts}}^2} \qquad (2)$$

u_{CRM} uncertainty of a certified value;

u_{char} uncertainty from the characterization of the batch

u_{bb} uncertainty due to the between – bottle inhomogeneity;

u_{sts} and u_{lts} are uncertainties due to the short - term and long – term instability.

* Assuming independence of the variables in Eq. 1

Introduction (2)

◆ Review of the model of ISO G 35 (Eq. 1)

$$x_{\mathrm{CRM}} = x_{\mathrm{char}} + \delta x_{\mathrm{bb}} + \delta x_{\mathrm{sts}} + \delta x_{\mathrm{lts}}$$

$$x_{\mathrm{CRM}} = x_{\mathrm{char}} + (x_{\mathrm{mean}} - x_{\mathrm{char}}) + (x_{\mathrm{sts}} - x_{\mathrm{char}}) + (x_{\mathrm{lts}} - x_{\mathrm{char}}) \qquad (3)$$

"*Usually, the homogeneity and stability study are designed in such a way that the error terms are zero and their uncertainties are not*" [1], x_{lts} and x_{sts} in Eq. (5) are neither obtained nor utilized in the calculation of the value of the CRM.

◆ Usual practice of chemists for CRM characterization

- At least 10 bottles selected from a batch
- Use a method with highest metrological quality to measure the selected bottles (once or multiple times per bottle) for simultaneous characterization and homogeneity assessment

* the stability terms are assumed to be zero for an initial certification (T=0)

$$x_{\mathrm{CRM}} = x_{\mathrm{char}} = x_{\mathrm{mean}} \qquad u(x_{\mathrm{mean}}) = u(x_{\mathrm{char}}) = \sqrt{u^2_{\mathrm{method}} + u^2_{\mathrm{bb}}} \Rightarrow u'_{\mathrm{char}}$$

$$u_{\mathrm{CRM}} = \sqrt{u^2_{\mathrm{char}} + u^2_{\mathrm{bb}} + u^2_{\mathrm{sts}} + u^2_{\mathrm{lts}}} = \sqrt{u'^2_{\mathrm{char}} + u^2_{\mathrm{sts}} + u^2_{\mathrm{lts}}} \qquad (4)$$

Park *et al.* Accred Qual Assur (2011) 16:263-266; Kim *et al.* Anal Bioanal Chem (2010) 398:1035–1042

General model and uncertainty evaluation

◆ General model of ISO G 35 (Eq. 1) with the consideration of long-term stability

$$Y = X(1 + b'T) \qquad (5)$$

Y = decreased value of CRM at a time T due to the degradation
X = initial value of CRM
= constant relative degradation rate as a function of time T
T = time elapsed since initial certification.

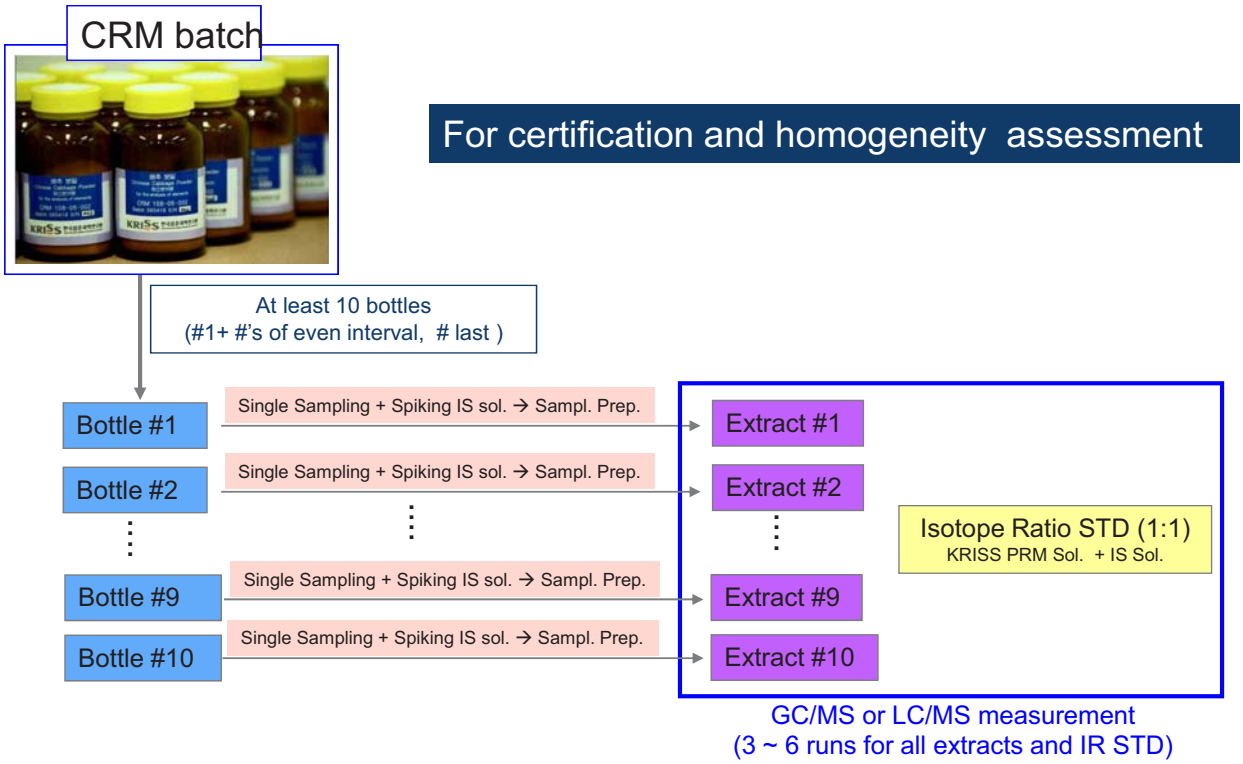
◆ Basic concept : Initial certification (characterization & homogeneity assessment)
➔ at T=0, $X = X_{\mathrm{CRM}} = X_{\mathrm{char}}$

◆ Uncertainty relationship

$$u_{\mathrm{CRM}} = \sqrt{u^2_{\mathrm{char}} + u^2_{\mathrm{bb}} + u^2_{\mathrm{sts}} + u^2_{\mathrm{lts}}} = \sqrt{u'^2_{\mathrm{char}} + u^2_{\mathrm{sts}} + u^2_{\mathrm{lts}}} \qquad (6)$$

$$u(x_{\mathrm{mean}}) = u(x_{\mathrm{char}}) = u'_{\mathrm{char}} = \sqrt{u^2_{\mathrm{method}} + u^2_{\mathrm{bb}}} \qquad (7)$$

Example of initial certification at $T = 0$



Example results from initial certification at $T = 0$

For certification and homogeneity assessment

Bottle No.	Concentration, X_j (mg/kg)	$u_{\text{method, A}}$ (mg/kg)	$u_{\text{method, B}}$ (mg/kg)	u_{method} (mg/kg)
1	0.4591	0.0021 (ν=3)	0.0035 (ν=12)	0.0040 (ν=14)
2	0.4576	0.0026 (ν=3)	0.0034 (ν=12)	0.0043 (ν=12)
3	0.4567	0.0023 (ν=3)	0.0034 (ν=12)	0.0041 (ν=14)
:	:	:	:	:
10	0.4534	0.0025 (ν=3)	0.0034 (ν=12)	0.0042 (ν=13)
Mean(X_{mean}) / Pooled uncertainty	0.4546	0.0026 (ν=30)	0.0034 (ν=12)	0.0043 (ν=26)
SD (S_{bb})	0.0045 (ν=9)			

$$u_{\text{method}} = \sqrt{u^2_{\text{method, A}} + u^2_{\text{method, B}}} \qquad (8)$$

Kim *et al.* Anal Bioanal Chem (2010) 398:1035–1042

Uncertainty evaluation for initial certification

$$u'_{char} = \sqrt{u^2_{\text{method}} + u^2_{\text{bb}}} = \sqrt{u^2_{\text{method,A}} + u^2_{\text{method,B}} + u^2_{\text{bb}}} \quad (9)$$

◆ u_{method} vs S_{bb} (between bottle standard deviation)

$$S_{\text{bb}} = \sqrt{s_r^2 / n + s^2_{\text{bb}}} = \sqrt{u^2_{\text{method,A}} + u^2_{\text{bb}}} \quad (10)$$

- s_r repeatability of the measurement method
- $u_{\text{method,A}}$ Type A uncertainty of the measurement method
  - ➔ $s_r / n = u_{\text{method, A}}$
  - ➔ $s_{\text{bb}} = u_{\text{bb}}$

Choi *et al.* Accred Qual Assur (2003) 8:13-15 & 205-207

◆ Calculation of u'_{char} from u_{method} and S_{bb}

$$u'_{\text{char}} = \sqrt{u^2_{\text{method,B}} + S^2_{\text{bb}}} \quad (11)$$

Example results from initial certification at T=0

For certification and homogeneity assessment

Bottle No.	Concentration, X_j (mg/kg)	$u_{\text{method, A}}$ (mg/kg)	$u_{\text{method, B}}$ (mg/kg)	u_{method} (mg/kg)
1 (12)	0.4591	0.0021 (ν=3)	0.0035 (ν=12)	0.0040 (ν=14)
2 (40)	0.4576	0.0026 (ν=3)	0.0034 (ν=12)	0.0043 (ν=12)
3 (68)	0.4567	0.0023 (ν=3)	0.0034 (ν=12)	0.0041 (ν =14)
:	:	:	:	:
10 (264)	0.4534	0.0025 (ν=3)	0.0034 (ν=12)	0.0042 (ν=13)
Mean(X_{mean}) / Pooled uncertainty	0.4546	0.0026 (ν=30) included $u_{\text{method,A}}$	0.0034 (ν=12) $u_{\text{method,B}}$	0.0043 (ν=26)
SD (S_{bb})	0.0045 (ν=9)			
Comb. $u(X_{\text{mean}})$	0.0057 (ν=17)	$u'_{\text{char}} = \sqrt{u^2_{\text{method,B}} + S^2_{\text{bb}}}$		
Expanded Uncertainty	0.0120 (k = 2.11, with 95 % level of confidence)			

Kim *et al.* Anal Bioanal Chem 398:1035–1042 (2010)

Pending issues in uncertainty of stability

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◆ General model of ISO G 35 (Eq. 1) with the consideration of long-term stability

$$Y = X(1 + b'T) \qquad (5)$$

$$u_{\mathrm{CRM}} = \sqrt{u_{\mathrm{char}}^2 + u_{\mathrm{bb}}^2 + u_{\mathrm{sts}}^2 + u_{\mathrm{lts}}^2} = \sqrt{u'^2_{\mathrm{char}} + u_{\mathrm{sts}}^2 + u_{\mathrm{lts}}^2}$$

◆ Usual practice for the stability assessment

- CRM production plan is designed that the stability terms are to be zero ($b' \cong 0$)
- Stability assessment is usually done by analyzing multiple bottles of the CRM by the method used for the initial certification
- Selecting transportation method/conditions to guarantee stability of the CRM ($u_{\mathrm{sts}} \approx 0$). Van der Veen *et al.* Accred Qual Assur (2001) 6:257-263

◆ Uncertainty of long-term stability in ISO G35

$$u_{\mathrm{lst}} = u(\mathrm{b}) \cdot XT$$

- u_{lts} in this equation contains s_{bb} and s_{r}
- In the absence of trend, u_{lts} is near to zero if s_{bb} and s_{r} are excluded

Cases for Long-term stability assessment

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Van der Veen *et al.* Accred Qual Assur (2001) 6:257-263

In cases, not significant statistically or otherwise relevant trend in the property value has been observed

◆ Isochronous stability study
- All measurement can be carried out in one run, with one calibration (goof repeatability)
- Problem : providing data at the end of study
  Instability at the reference temperature is not guaranteed

◆ Classical stability study
- Measuring sample as a function of time
- Problem : need to be carried out under reproducible conditions

◆ Stability monitoring

$$\left|X_{\mathrm{CRM}} - X_{\mathrm{meas}}\right| \le k\sqrt{u_{\mathrm{CRM}}^2 + u_{\mathrm{meas}}^2}$$

- Using classical design
- Reconfirming validity of the CRM (X and u_{CRM}) at T
- Information becomes available during the lifetime of the CRM
- Better to use a method which has the same metrological quality with the one used for the initial certification
- Data can be used for re-evaluation of u_{CRM}

◆ Semi-continuous stability testing

◆ With prior knowledge of long-term stability of a specific type of CRM
- In absence of trend, u_{lts} can be set to zero
- Still, stability monitoring is needed to be carry out.

Conclusion

- Model for uncertainty evaluation of CRM is proposed for simultaneously assessing property value and inhomogeneity
- Basic model $Y = X$ is derived from the general model $Y = X(1+b´T)$ as the special case of $T=0$, instead of $x_{\mathrm{CRM}} = x_{\mathrm{char}} + \delta x_{\mathrm{bb}} + \delta x_{\mathrm{sts}} + \delta x_{\mathrm{lts}}$
- u_{bb} is shown to be one of the uncertainty components of x_{char}
- Uncertainty due to instability of the CRM can be evaluated in many ways depending on the situations, and further discussion is needed in metrology community