Past and future impact of statistical software proposed by Arlenda for the validation and transfer of analytical methods

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1. Aim of Analytical Method Validation and Transfer

2. The Past:
   1. Traditional Analytical Method Validation
   2. Is my Method Valid?

3. The Present:
   1. Rewarding Analytical Method Validation
   2. Applicability?

4. The Future:
   1. Link results reliability to decisions trustiness
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Analytical Methods

No direct quantification!

Concentration ($X$) = ?

Needs calibration…:

… to obtain concentration ($X$):
Analytical Method Life Cycle

• What is the final aim of quantitative analytical methods?
  – Start with the end!
  – Objective: provide results used to make decisions
    • Release of a batch
    • Stability/Shelf life
    • Patient health
    • PK/PD studies, …

• What matters are the results produced by the method.
Analytical Method Life Cycle

- Selection
- Development
- Routine Use
- Validation

Life Cycle

Guarantees ?
Reliability ?
Analytical Method Life Cycle

• Need to demonstrate/guarantee that the analytical method will provide, in its future routine use, quality results

• This is the key aim of Analytical Method Validation!

How?
Aim of transfer

Is to give **guaranties** that the results of the « receiving lab. » **will be close enough** to the **true value** in order to **minimise the risks** to take a wrong decision.
Aim of transfer

By opposition to validation, the true value $\mu_T$ of the sample is unknown but is estimated by the « sending » lab with uncertainty.

→ During “Transfer” assessment the uncertainty linked to this estimation must be included.
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Analytical Method Validation

• Traditional vision:
  – The Validation Criteria Check List:
    • Selectivity
    • Trueness/Mean Accuracy
    • Precision
    • Linearity
    • Range
    • Limit of Quantification (LOQ)

Method Valid!
Analytical Method Validation

• Traditional vision:
  – Is a valid method providing reliable results?

Analytical Method

Bias

% Bias < 3%

Precision

% CV < 2%

Analytical Results

Are you ready to take this risk?
Analytical Method Validation

• Traditional vision:
  – Preliminary Conclusion:

  “Good” Methods do **NOT** necessarily provide “good” Results!
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Decision Methodology

• How to decide about methods’ validity?

• Do we need statistics?

• If yes, what statistical methodology?

➡ Let’s illustrate this through an example:
Example

• Validation of HPLC-UV method for the quantification of codeine and paracetamol in a drug product

• Design:
  – 3 series,
  – 3 repetitions per series for the validation standards
  – 3 concentration levels for the validation standards
Traditional Approaches:

**Separate** evaluation of methods **Trueness** and **Precision** and comparison to predefined acceptance limits ($\lambda$).

- **Descriptive:**
  - **trueness**: only based on estimation of method *bias*;
  - **precision**: only based on estimation of method $RSD_{I.P.}$.

- **Difference:**
  - **trueness**: based on bilateral Student t-test for *bias* significance.

- **Equivalence:**
  - **trueness**: based on confidence interval of the *bias* ($=TOST$);
  - **precision**: based on confidence interval of the intermediate precision variance.

How to decide?
Descriptive Approach

Trueness:

Precision:

Bias (%) → 0 → ̂δ → +λ_{Tru} → -λ_{Tru}

RSD (%) → 0 → RSD_{l.P.} → +λ_{Pre} → +λ_{Pre}
**Example**

**Trueness**

- **Paracetamol**
  - 200 µg/ml: -1.2
  - 400 µg/ml: -0.1
  - 600 µg/ml: -0.2

- **Codeine**
  - 20 µg/ml: 0.1
  - 25 µg/ml: -0.6
  - 30 µg/ml: -0.4

**Precision**

- **Paracetamol**
  - 200 µg/ml: 1.8
  - 400 µg/ml: 1.0
  - 600 µg/ml: 0.3

- **Codeine**
  - 20 µg/ml: 0.3
  - 25 µg/ml: 0.8
  - 30 µg/ml: 1.0

**Notes:**
- Trueness values range from -2% to +2%.
- Precision values range from 0% to +3%.

**Chemicals:**
- Paracetamol
- Codeine
Descriptive: performance

\[ X_{ij} = \mu + \alpha_i + \varepsilon_{ij} \]

with \( \alpha_i \sim iN(0, \sigma^2_{\alpha}) \),
\( \varepsilon_{ij} \sim iN(0, \sigma^2_{\varepsilon}) \),
\( R = \frac{\sigma^2_{\alpha}}{\sigma^2_{\varepsilon}} \)
\( \lambda_{\text{just}} = \pm 2\% \)
\( \lambda_{\text{Fid}} = 3\% \)

55% risk


Valid methods but Poor results
Difference Approach

\[ H_0 : \delta = 0 \]
\[ H_1 : \delta \neq 0 \]

No rejection of \( H_0 \) \( \Rightarrow \) Method **valid !?**

Rejection of \( H_0 \) \( \Rightarrow \) Method **not valid !?**
Difference: performance

Equivalence Approach

**Trueness:**

- $-\lambda_{\text{Tru}}$
- $\delta$
- $+\lambda_{\text{Tru}}$

Confidence Interval (C.I.) of the bias

**Precision:**

- $0$
- $RSD_{I.P.}$
- $+\lambda_{\text{Pre}}$

Upper Limit of the $RSD_{I.P}$ C.I.
Example

**Trueness**

- **Paracetamol**
  - 200 µg/ml
  - 400 µg/ml
  - 600 µg/ml

- **Codeine**
  - 20 µg/ml
  - 25 µg/ml
  - 30 µg/ml

**Precision**

- 1.8
- 1.0
- 0.3
- 0.3
- 1.0
- 0.8
- 1.0

-2% 0 +2% 0 +3%
Equivalence: performance

\[ X_{ij} = \mu + \alpha_i + \varepsilon_{ij} \]
with \( \alpha_i \sim iN(0, \sigma_\alpha^2) \),
\( \varepsilon_{ij} \sim iN(0, \sigma_\varepsilon^2) \),
\( R = \sigma_\alpha^2 / \sigma_\varepsilon^2 \)
\( \lambda_{\text{just}} = \pm 2\% \)
\( \lambda_{\text{Fid}} = 3\% \)

Valid methods but Poor results

Summary

• Descriptive approach:
  – no risk management
  – Up to 50% risk to take wrong decision

• Difference approach:
  – Useless for Method Validation purpose: Avoid it!

• Equivalence approach
  – Patient risk controlled
  – Nonetheless do not fully answer method validation aim: the method is “good” but not necessarily the results!
• Is there any better decision methodology?
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Aim of validation
Is to give to laboratories as well as to regulatory agencies the guaranties that each result that will be obtained in routine will be close enough to the unknown true value of the analyte in the sample.

\[ \pi = P \left( \left| X_i - \mu_T \right| < \lambda \right) \geq \pi_{\text{min}} \]

\( \lambda \) = predefined acceptance limits
\( \pi_{\text{min}} \) = minimum probability that a result will be included inside \( \pm \lambda \)

Aim of Analytical Method Validation

The aim of validation is evaluating whether the probability that each future result will be included within predefined acceptance limits is acceptable. Based on the estimations of method’s bias and precision.

\[
E_{\hat{\delta}, \hat{\sigma}} \left\{ P \left[ \left| X_i - \mu_T \right| < \lambda \right] \left| \hat{\delta}, \hat{\sigma} \right\} \geq \pi_{\text{min}} \right.
\]
Aim of Analytical Method Validation

The aim of validation is evaluating whether the probability that each future result will be included within the acceptance limits. Based on the estimations of bias and precision.

\[ E_{\hat{\delta}, \hat{\sigma}} \left\{ P \left[ \left| X_i - \mu_T \right| < \lambda \right] \right\} \geq \pi_{\text{min}} \]

Accuracy (total error) required of each future result
The aim of validation is evaluating whether the probability that each future result will be included within the acceptance limits.

Based on the estimation of bias and precision.

\[ E_{\hat{\delta}, \hat{\sigma}} \left\{ P \left[ \left| X_i - \mu_T \right| < \lambda \right] \right\} \geq \pi_{\text{min}} \]

Accuracy (total error) required of each future result

Missing Link

Estimators of the method performances obtained during the validation phase
Summary of the aims

Aims

- Each single future result / not the past results.

- Futur results / not the method performances.

- The past performances of the method are useless to take a decision even if they provide information about the method.

- Important to clarify the way the decision will be taken based on the results available.
Tolerance Intervals

**β-Expectation Tolerance Interval** (βTI)

Allows to predict where each future result will fall (Wald, 1942).

⇒ If the β-expectation tolerance interval is included inside the acceptance limits, then the probability that each future result will be within the acceptance limits is at least $\beta$ (ex. 80%).

*B. Boulanger et al., J. Chromatogr. B, 877 (2009) 2235*
\( X_{ij} = \mu + \alpha_i + \epsilon_{ij} \)
with \( \alpha_i \sim iN(0, \sigma_{\alpha}^2) \),
\( \epsilon_{ij} \sim iN(0, \sigma_{\epsilon}^2) \),
\( R = \sigma_{\alpha}^2 / \sigma_{\epsilon}^2 \)
\( \lambda_{\text{Just}} = \pm 2\% \)
\( \lambda_{\text{Fid}} = 3\% \)
\( \beta = 0.95 \)

Bouabidi et al., *J. Chromatogr. A*, 1217, (2010), 3180-3192
Accuracy Profile

Validation experiments

\[ \text{Bias} \]
\[
\text{bias}_j = \hat{\mu}_j - \bar{x}_j.
\]

\[ \text{Intermediate Precision} \]
\[
\hat{\sigma}^2_{W,j} + \hat{\sigma}^2_{B,j}
\]

Total error

\[ E_{\mu,\sigma} \left\{ \Pr \left[ |x_i - \mu| < \lambda \right] / \hat{\mu}, \hat{\sigma} \right\} \geq \beta \]

Predictive Interval with a known risk

\[ TL_B = \frac{(\bar{x}_c - \bar{x}_i) \pm k \cdot s_{IP}}{\bar{x}_i} \cdot 100 \]

\[ \lambda = \text{acceptance limits of e.g. 5\%} \]
Paracetamol

200 µg/ml

400 µg/ml

600 µg/ml

-5%  β = 0.95  +5%

Codeine

20 µg/ml

25 µg/ml

30 µg/ml

-5%  β = 0.95  +5%

Example
Example

Paracetamol

Codeine
Analytical Method Validation

Analytical Results

Analytical Method

Bias

% Bias < 3%

Precision

% RSD < 2%
Analytical Method Validation

• Accuracy Profile Approach:
  – Preliminary Conclusion:

  "Good" Results can only be obtained by "good" Methods!

  – Make a decision on the results, the very reason of an analytical quantitative method.
  – This way, it will guarantee your method is valid.
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Use of accuracy profiles

e.noval & Seelva

136 publications

Publications with accuracy profiles since 2001

From Scopus database
Use of accuracy profiles

- Countries using Accuracy profiles
Use of accuracy profiles
e.noval & Seelva

- What analytical techniques:
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Future

- **Switch** from the traditional check list validation & transfer to rewarding, useful and predictive approaches.

- Provide methodologies to declare methods valid or transferable by controlling the risks of erroneous decisions.
Future

- Validating analytical methods for content assays and quantitative impurity assays:
  - making the correct decision about product compliance with respect to their specification limits.

Future

- Validating analytical methods involved in dissolution assays.

Future

- Evaluating the reliability of analytical results using a probability criterion: A Bayesian perspective.

Future

- Validating analytical methods for Uniformity of Dosage Units

Decision profile

Unreliability regions

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Conclusions

- **Switch** from the traditional check list validation to a rewarding, useful and predictive method validation

- The **quality of future results** ($\approx \pi$) must be the objective and not the past performances of the method.

- The **$\beta$-expectation tolerance interval/Accuracy profile** fulfills this objective.
Conclusions

- The difference between validation and transfer resides only in the acceptance limits → **harmonised approach**.

- In such a way, the **risks** are known at the end of the validation.

- **Universal** methodology applicable to **any** quantitative assay.
Thanks for your attention

• Check our publications at:
  http://orbi.ulg.ac.be/

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