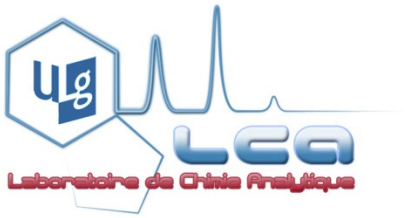

UNIVERSITE de LIEGE

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

E. Rozet

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Louvain-la-Neuve **September 24, 2013**

Content

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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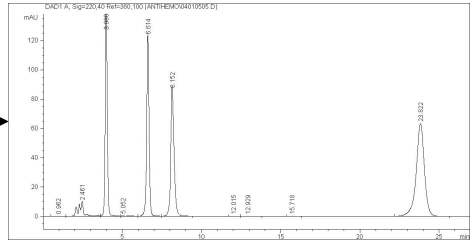
Analytical Methods

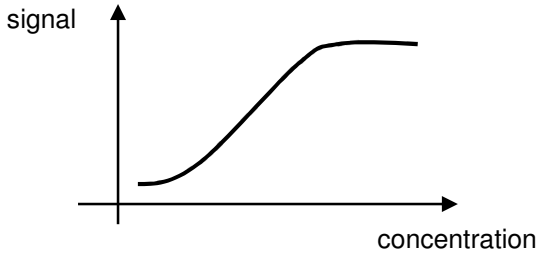
No direct quantification !



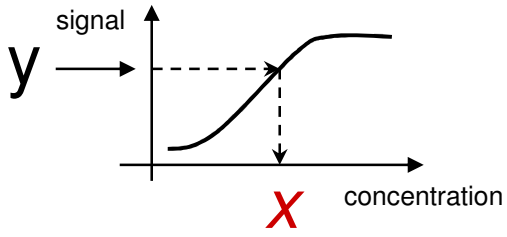
Concentration (***X***) = ?

signal = y

Needs calibration…:



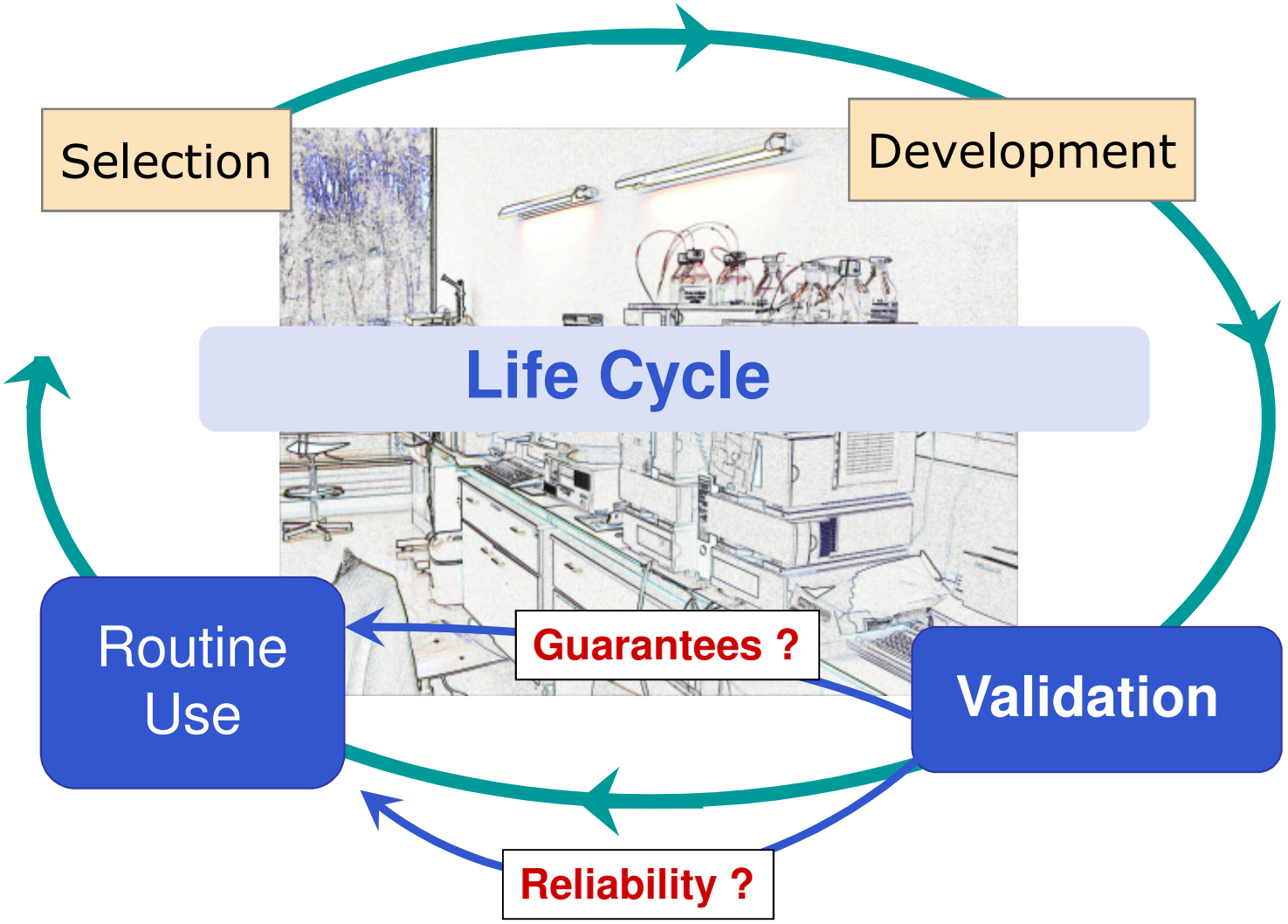
… to obtain concentration (***X***):



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



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

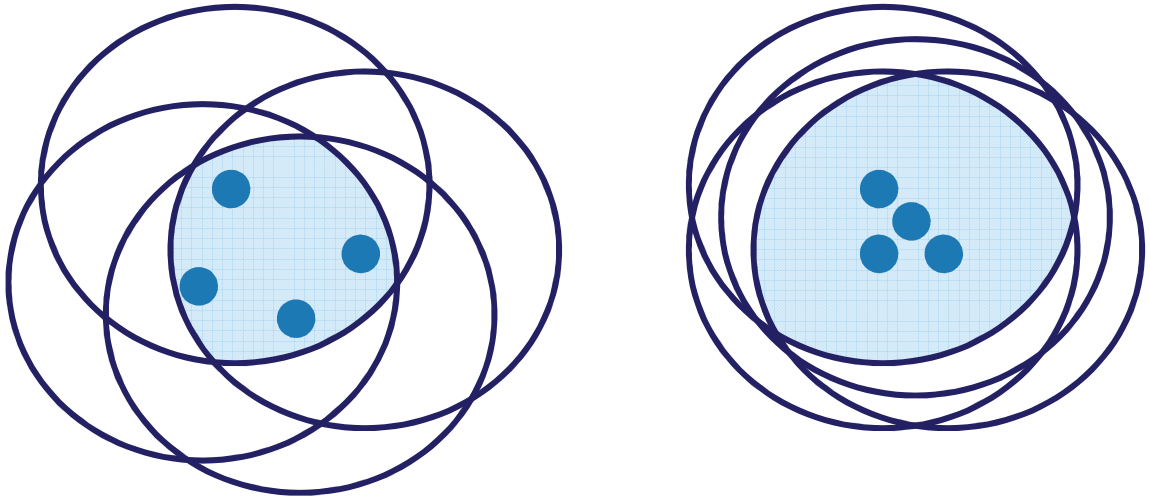
Aim of transfer

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 μ_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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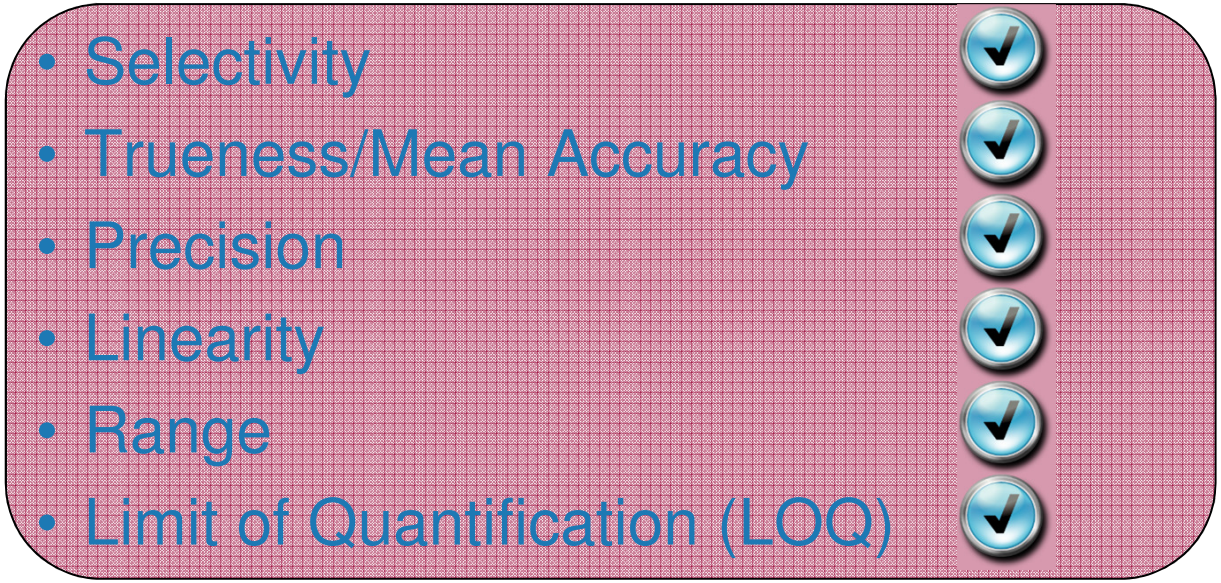
Analytical Method Validation

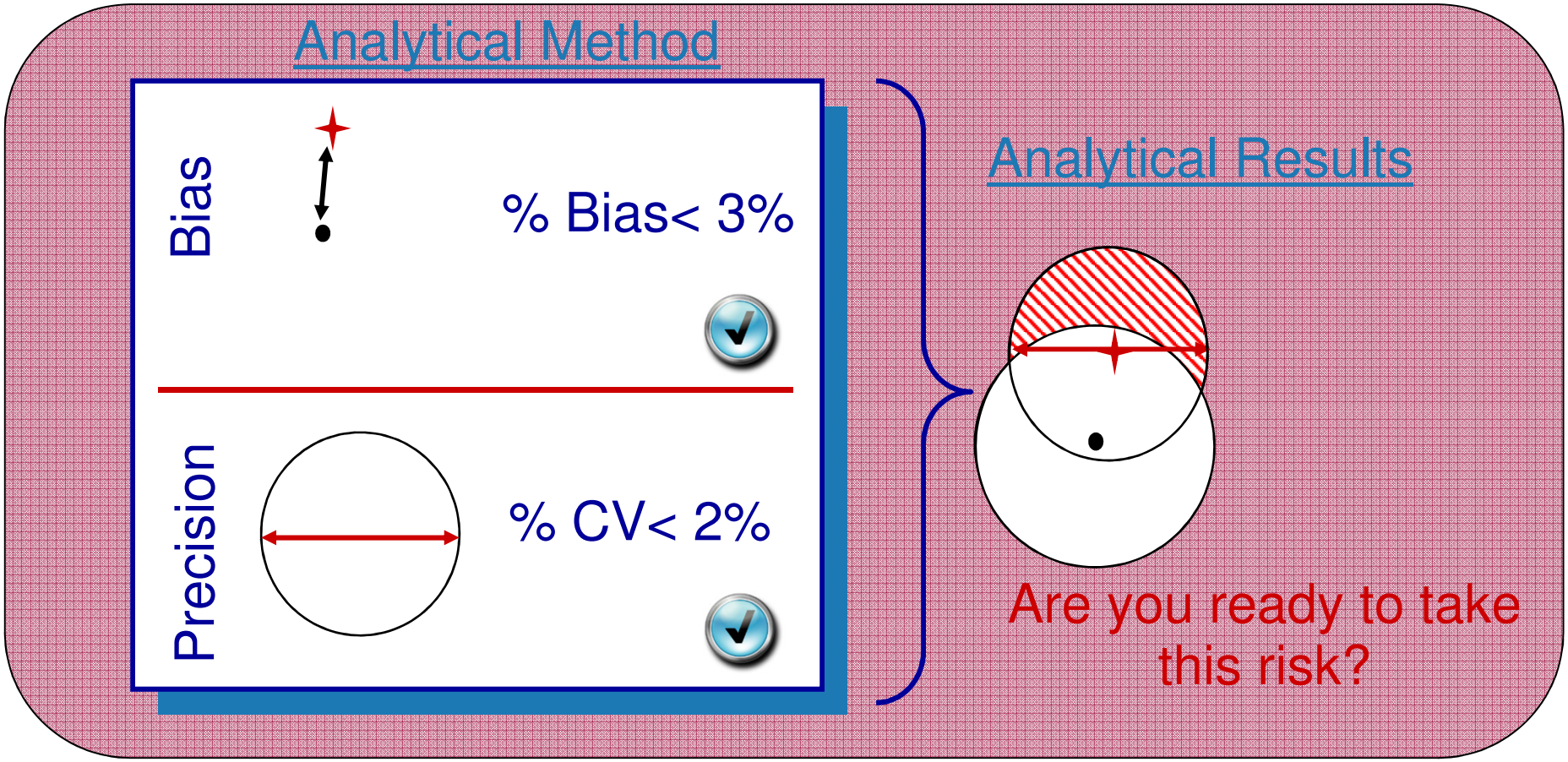
- Traditional vision:
  - The Validation Criteria Check List:



Method Valid !

Analytical Method Validation

- Traditional vision:
  - Is a valid method providing reliable results ?



Analytical Method Validation

- Traditional vision:
  - Preliminary Conclusion:

"**Good**" Methods do **NOT** necessarily provide "**good**" Results !

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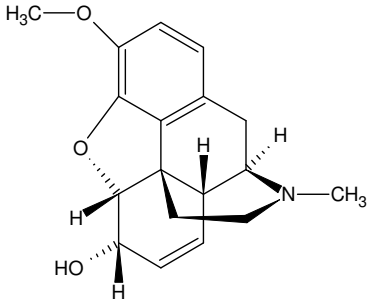
Decision Methodology

- How to decide about methods' validity ?
- Do we need statistics ?
- If yes, what statistical methodology ?

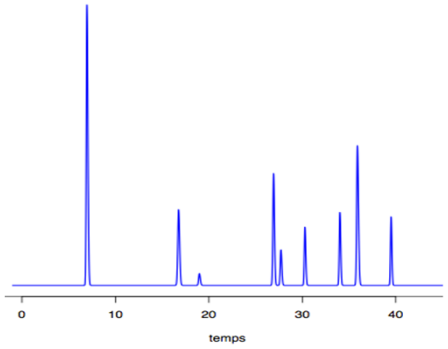
➔ Let's illustrate this through an example:

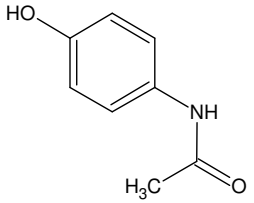
Example

- 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





How to decide ?

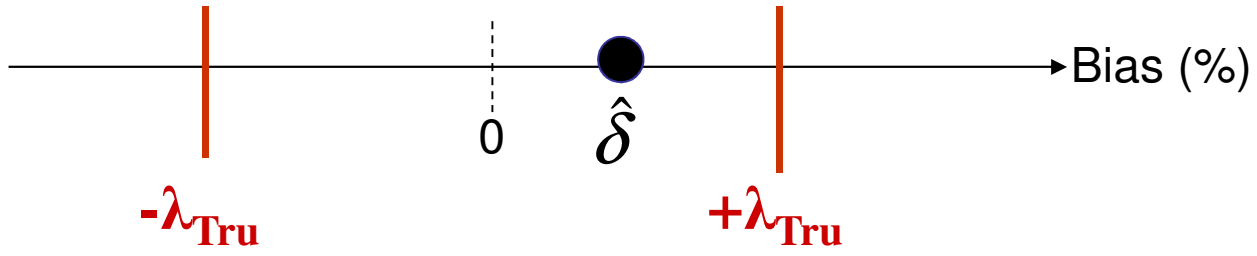
Traditional Approaches:

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

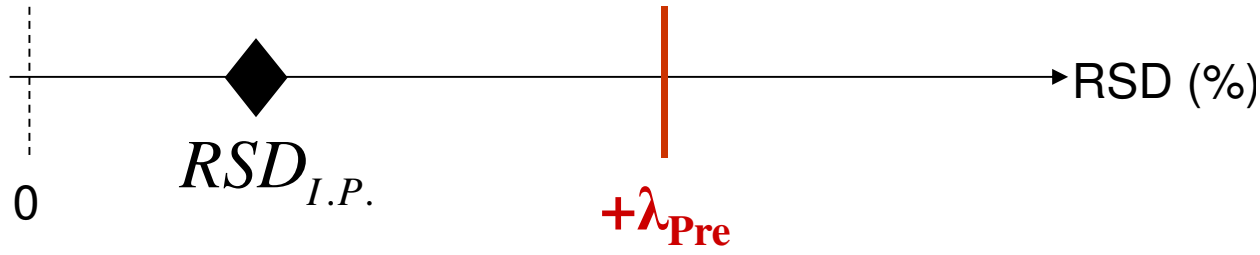
- Descriptive:
  - **trueness**: only based on estimation of method *bias*;
  - **precision**: only based on estimation of method $RSD_{I.P.}$.
- Difference:
  - **trueness**: based on bilateral Student t-test for *bias* significance.
- Equivalence:
  - **trueness**: based on confidence interval of the *bias (=TOST)*;
  - **precision**: based on confidence interval of the intermediate precision variance.

Descriptive Approach

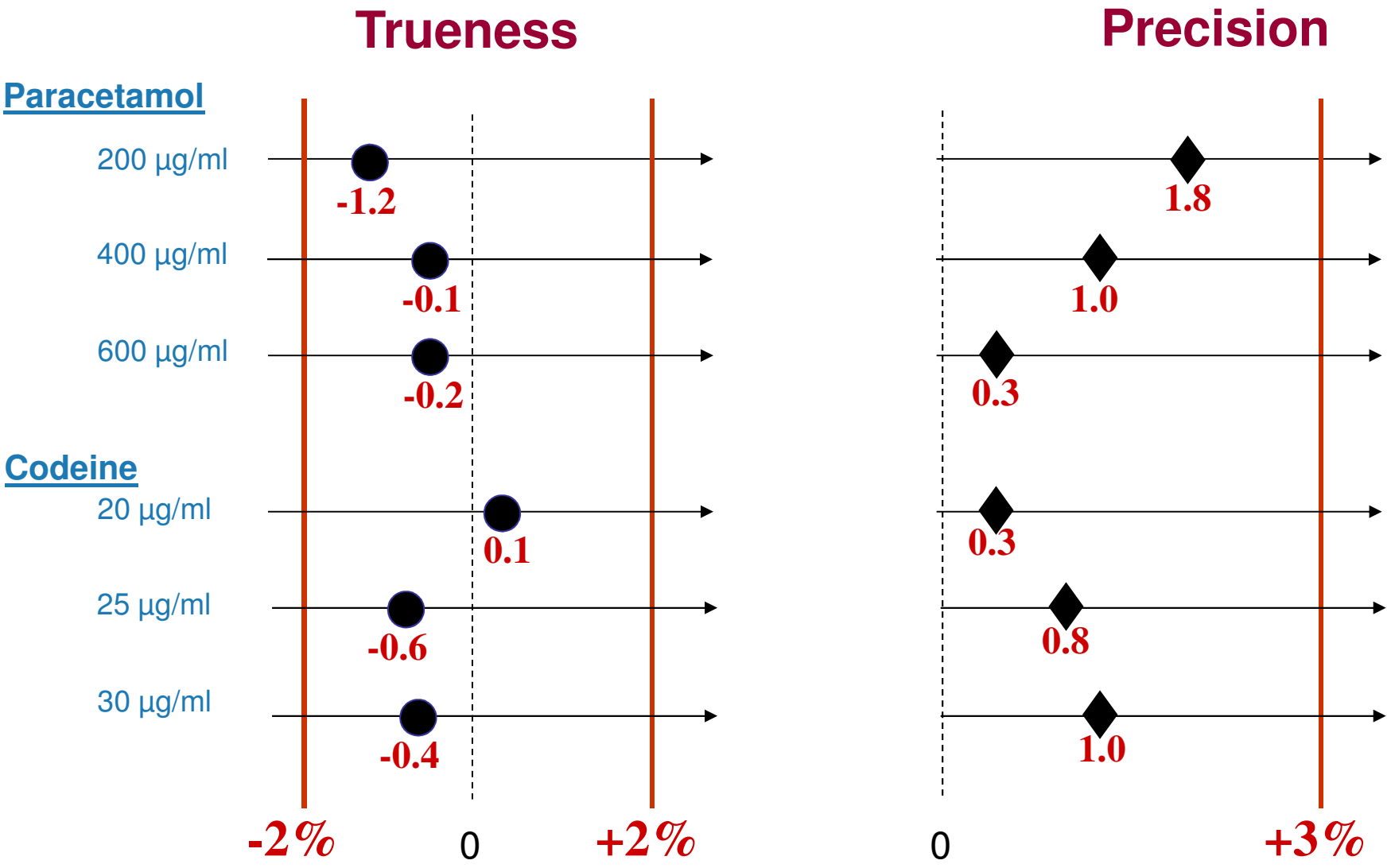
Trueness:



Precision:



Example


Trueness
Precision
Paracetamol
200 µg/ml
400 µg/ml
600 µg/ml
Codeine
20 µg/ml
25 µg/ml
30 µg/ml
-1.2
-0.1
-0.2
0.1
-0.6
-0.4
1.8
1.0
0.3
0.3
0.8
1.0
-2%
0
+2%
0
+3%

Descriptive: performance

$$X_{ij} = \mu + \alpha_i + \varepsilon_{ij}$$

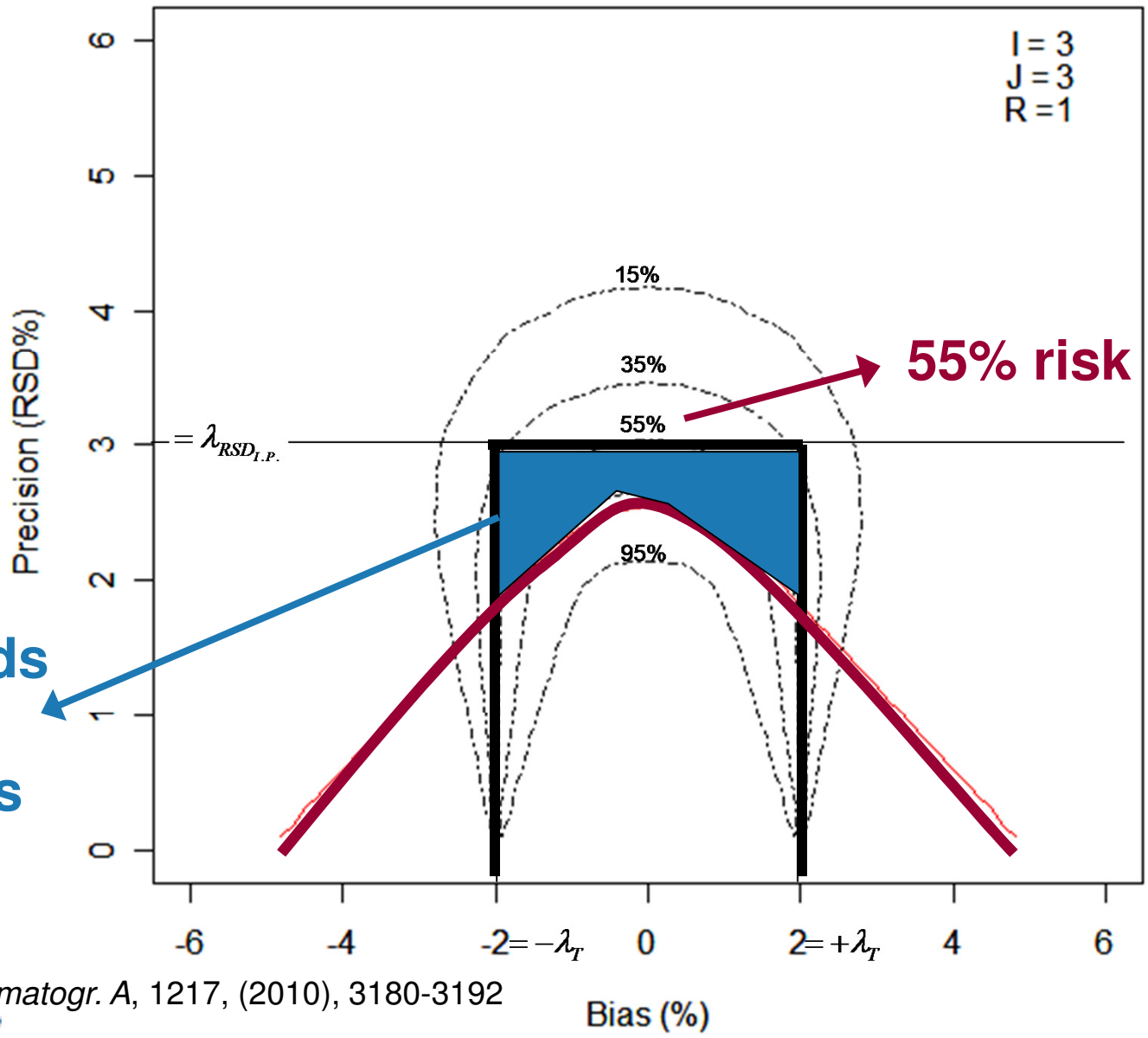
with $\alpha_i \sim iN(0, \sigma_\alpha^2)$,

$\varepsilon_{ij} \sim iN(0, \sigma_\varepsilon^2)$,

$R = \sigma_\alpha^2 / \sigma_\varepsilon^2$

$\lambda_{Just} = \pm 2\%$

$\lambda_{Fid} = 3\%$



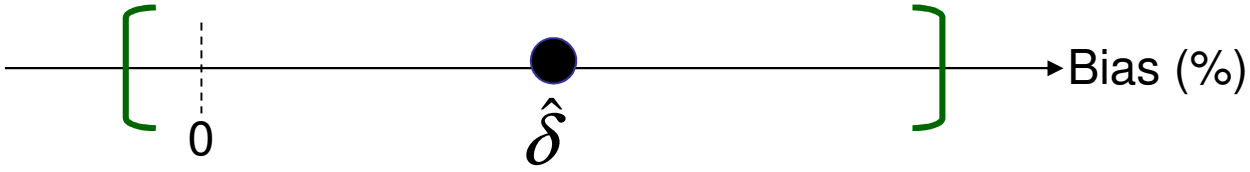
Valid methods but Poor results

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

Difference Approach

$$H_0 : \delta = 0$$

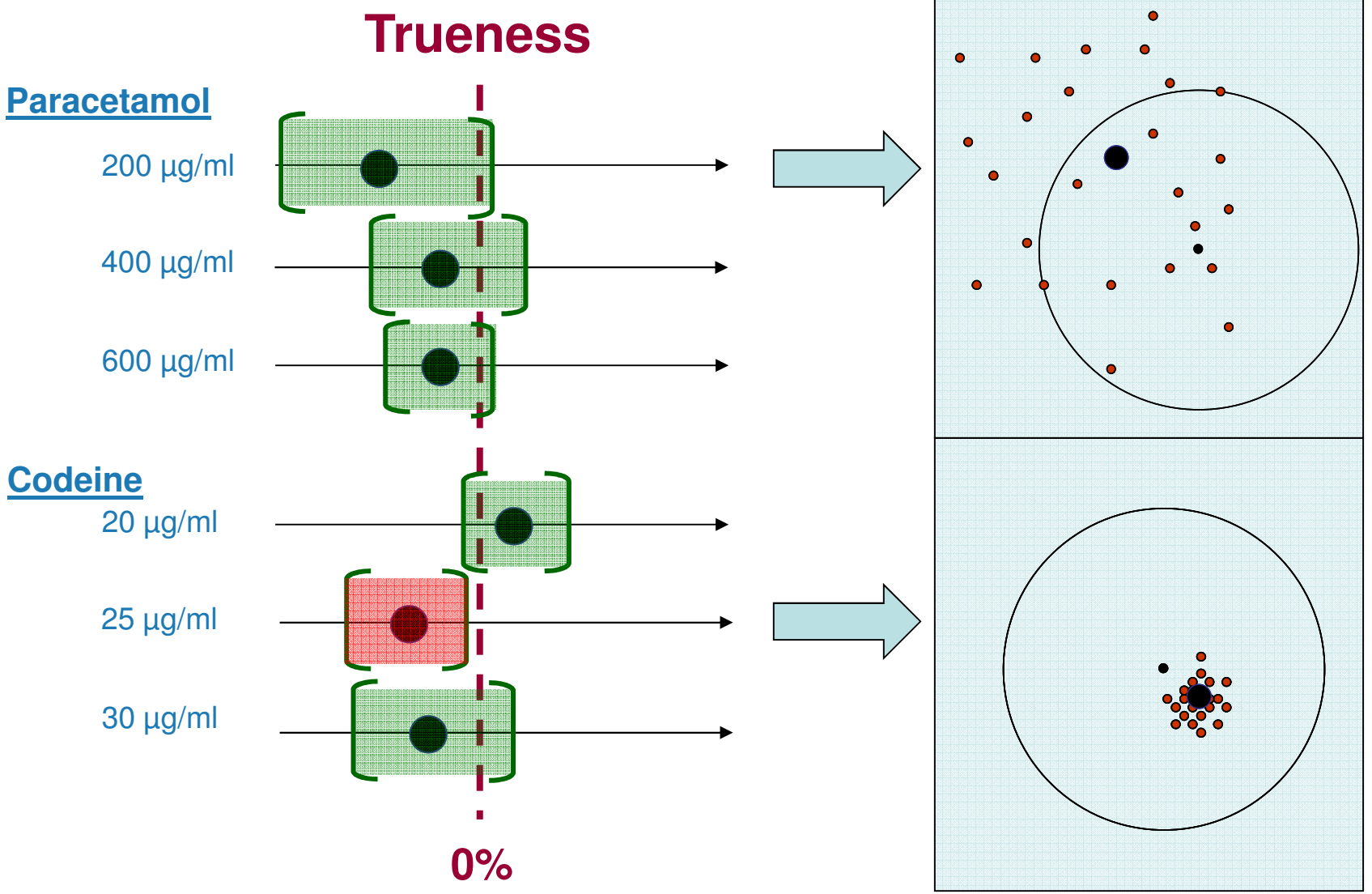
$$H_1 : \delta \neq 0$$



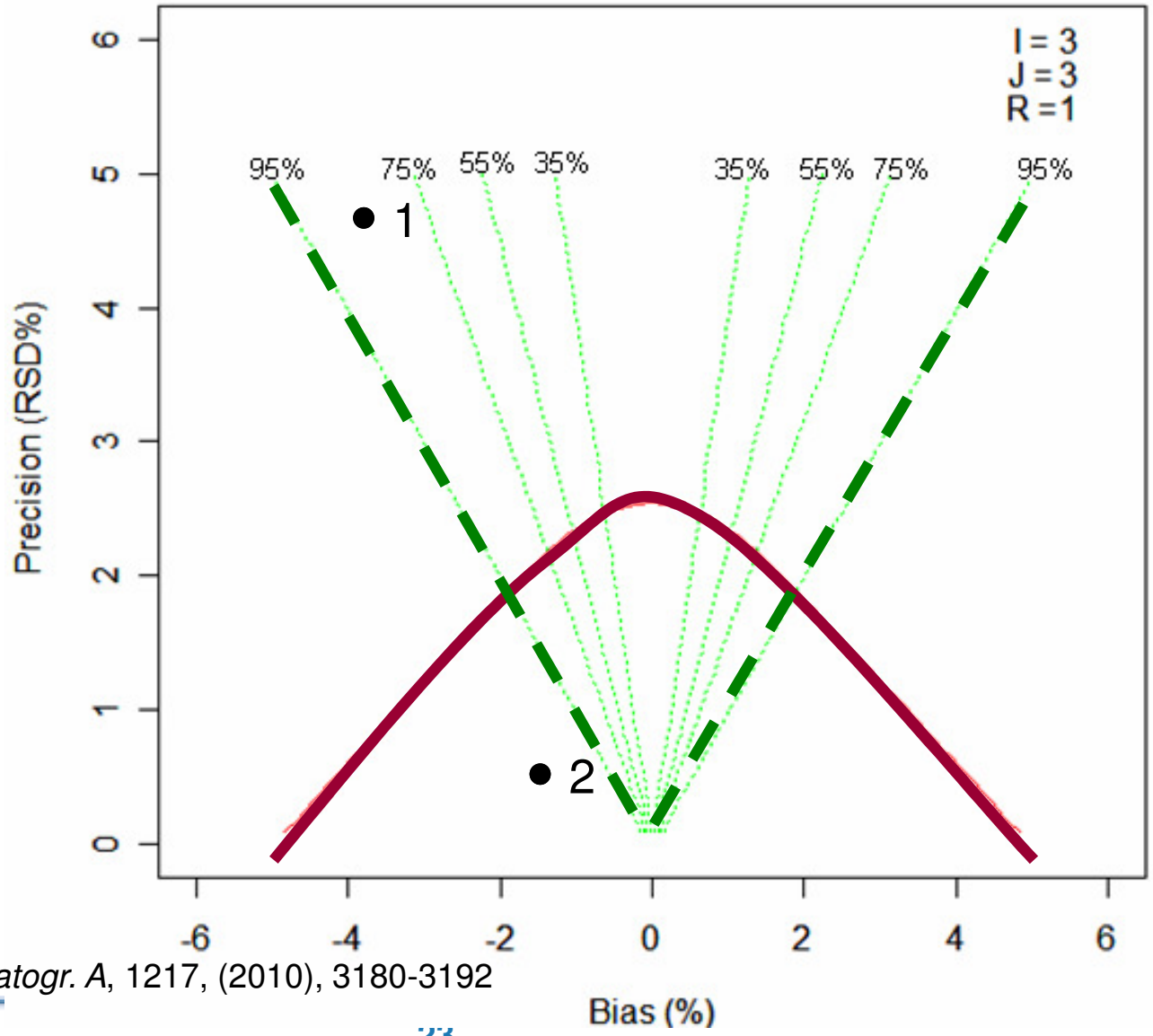
No rejection of H_0 ➔ Method **valid !?**

Rejection of H_0 ➔ Method **not valid !?**

Example


Trueness
Paracetamol
200 µg/ml
400 µg/ml
600 µg/ml
Codeine
20 µg/ml
25 µg/ml
30 µg/ml
0%

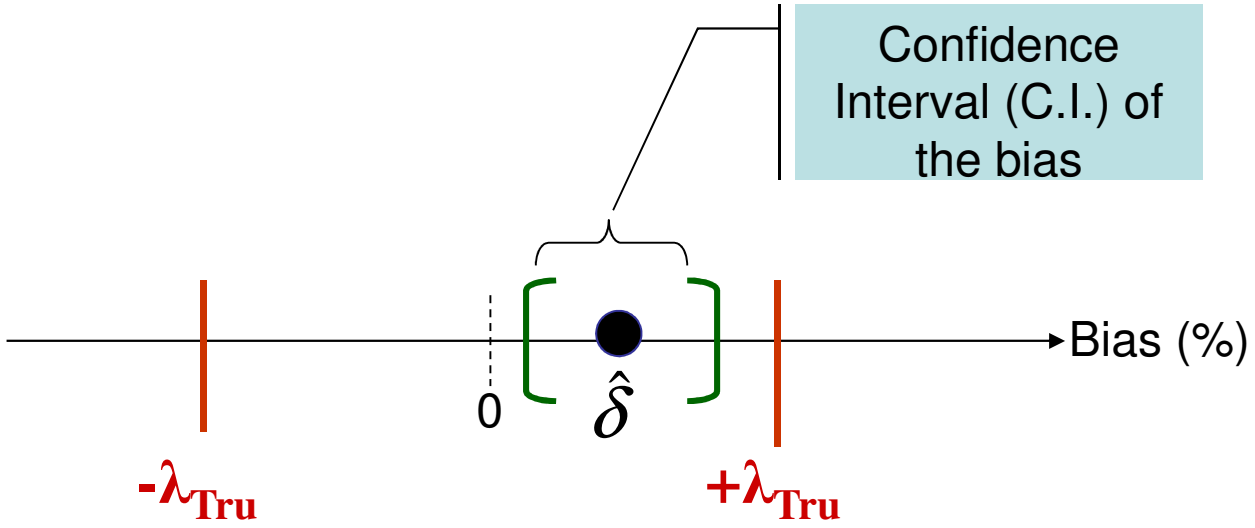
Difference: performance



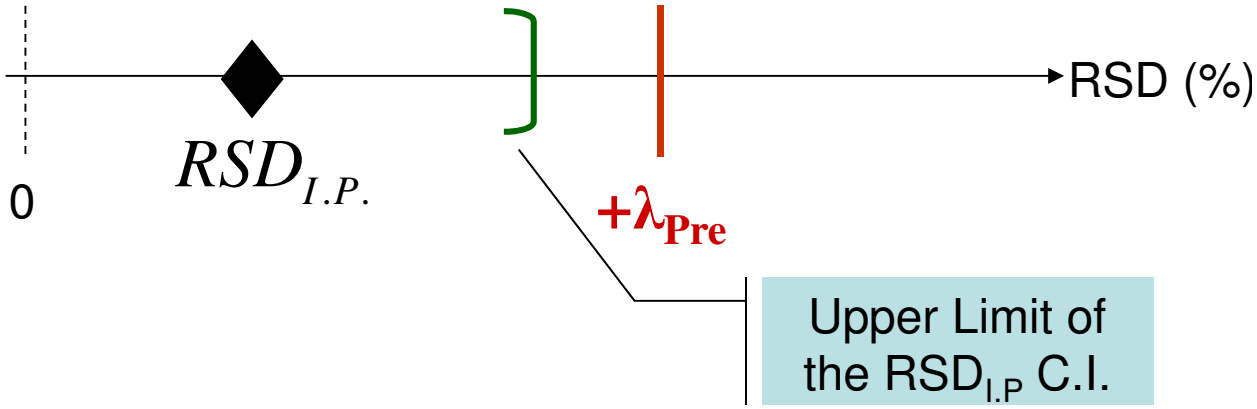
Bouabidi *et al.*, *J. Chromatogr. A*, 1217, (2010), 3180-3192

Equivalence Approach

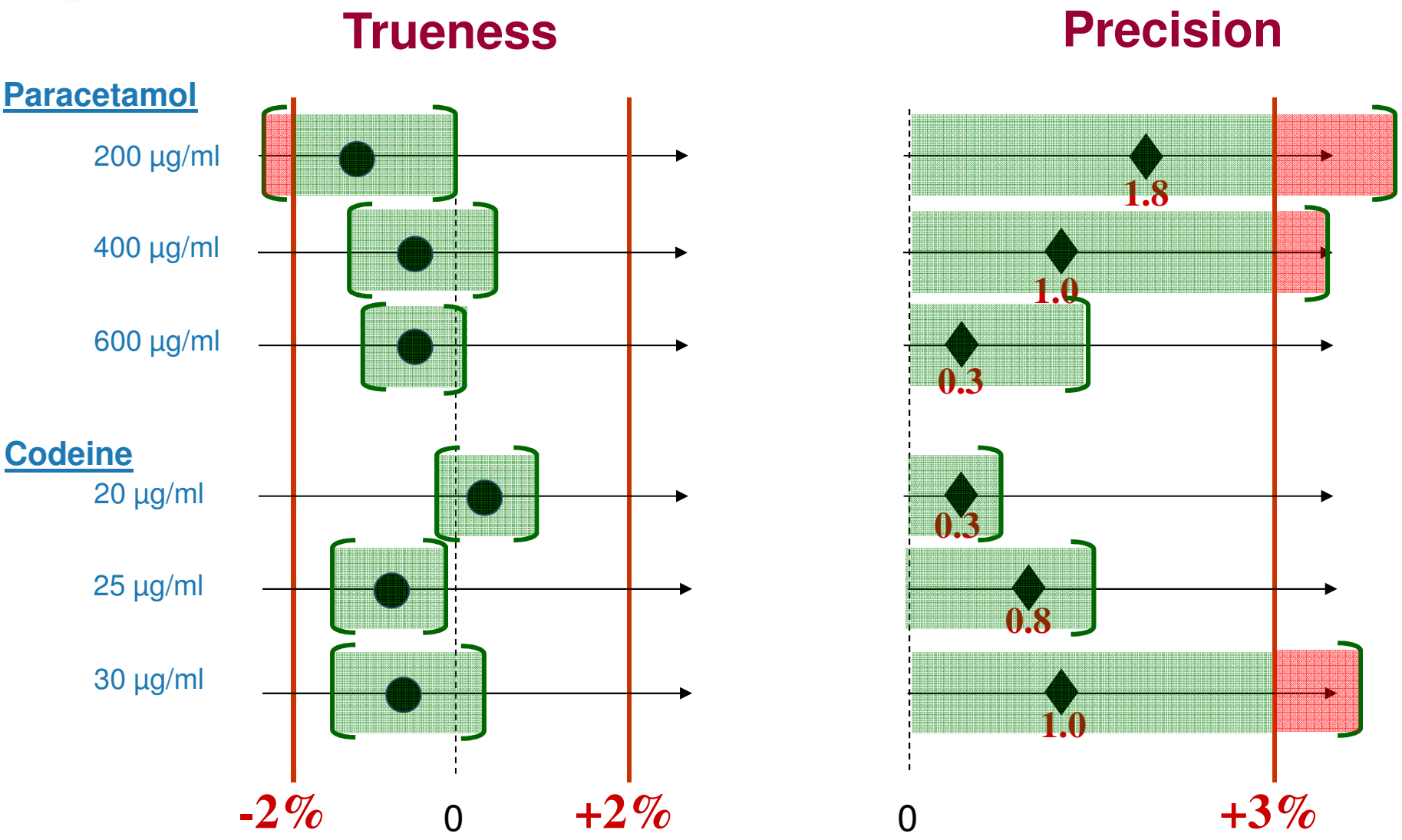
Trueness:



Precision:



Example


Trueness
Precision
Paracetamol
200 µg/ml
400 µg/ml
600 µg/ml
Codeine
20 µg/ml
25 µg/ml
30 µg/ml
1.8
1.0
0.3
0.3
0.8
1.0
-2%
0
+2%
0
+3%

Equivalence: performance

$$X_{ij} = \mu + \alpha_i + \varepsilon_{ij}$$

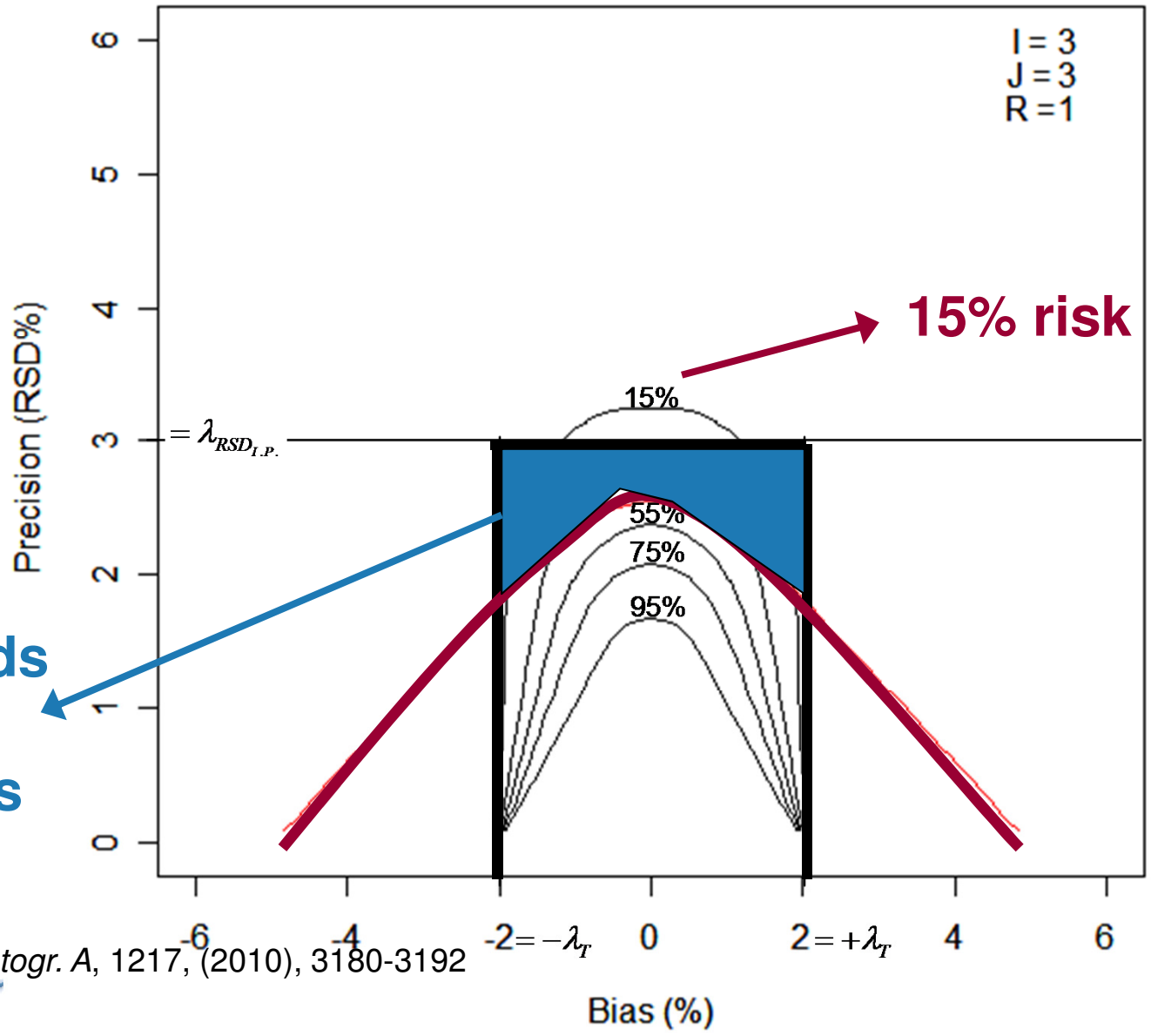
with $\alpha_i \sim iN(0, \sigma_\alpha^2)$,

$\varepsilon_{ij} \sim iN(0, \sigma_\varepsilon^2)$,

$R = \sigma_\alpha^2 / \sigma_\varepsilon^2$

$\lambda_{Just} = \pm 2\%$

$\lambda_{Fid} = 3\%$



Valid methods but Poor results

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

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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Analytical Method Validation

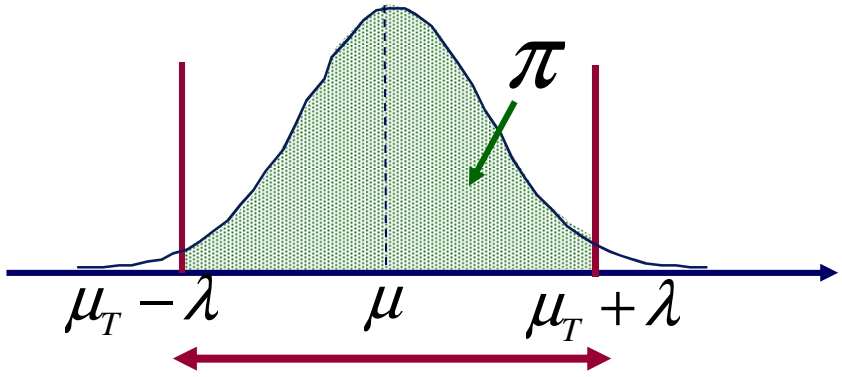
Aim of validation

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.

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

λ= predefined acceptance limits

π_{min}= minimum probability that a result will be included inside ± λ



E. Rozet et al., J. Chromatogr.A, 1158 (2007) 126

Aim of Analytical Method Validation

The aim of **validation** is evaluting 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.

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

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.

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

Accuracy (total error) **required** of each future result

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 **estimation of bias and precision.**

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

Accuracy (total error) **required** of each future result

?

Estimators of the **method performances** obtained during the **validation** phase

Missing Link

Summary of the aims

Aims

➔ Each single future result / not the past results.

➔ Futur results / not the method performances.

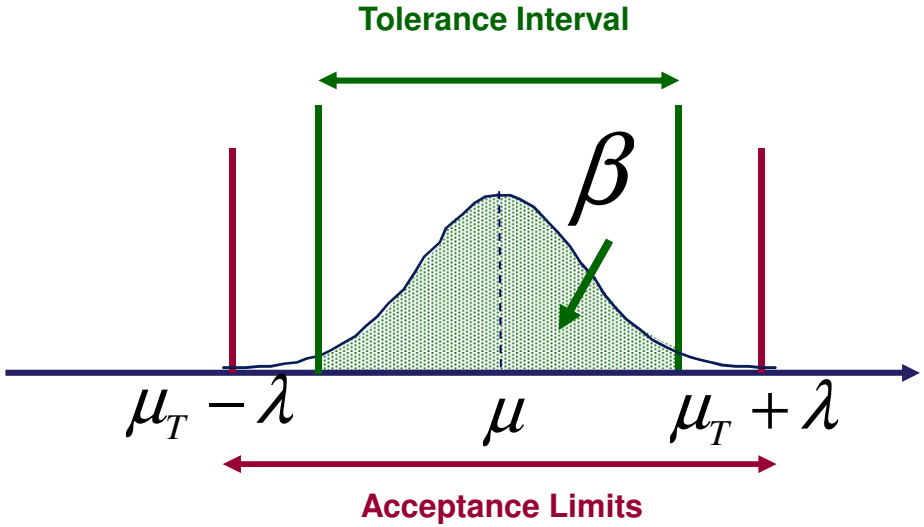
➔ The past performances of the method are useless to take a decision even if they provide information about the method.

➔ **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** β (ex. 80%).

B. Boulanger et al., J. Chromatogr. B, 877 (2009) 2235

βTI : performance

$$X_{ij} = \mu + \alpha_i + \varepsilon_{ij}$$

with $\alpha_i \sim iN(0, \sigma_\alpha^2)$,

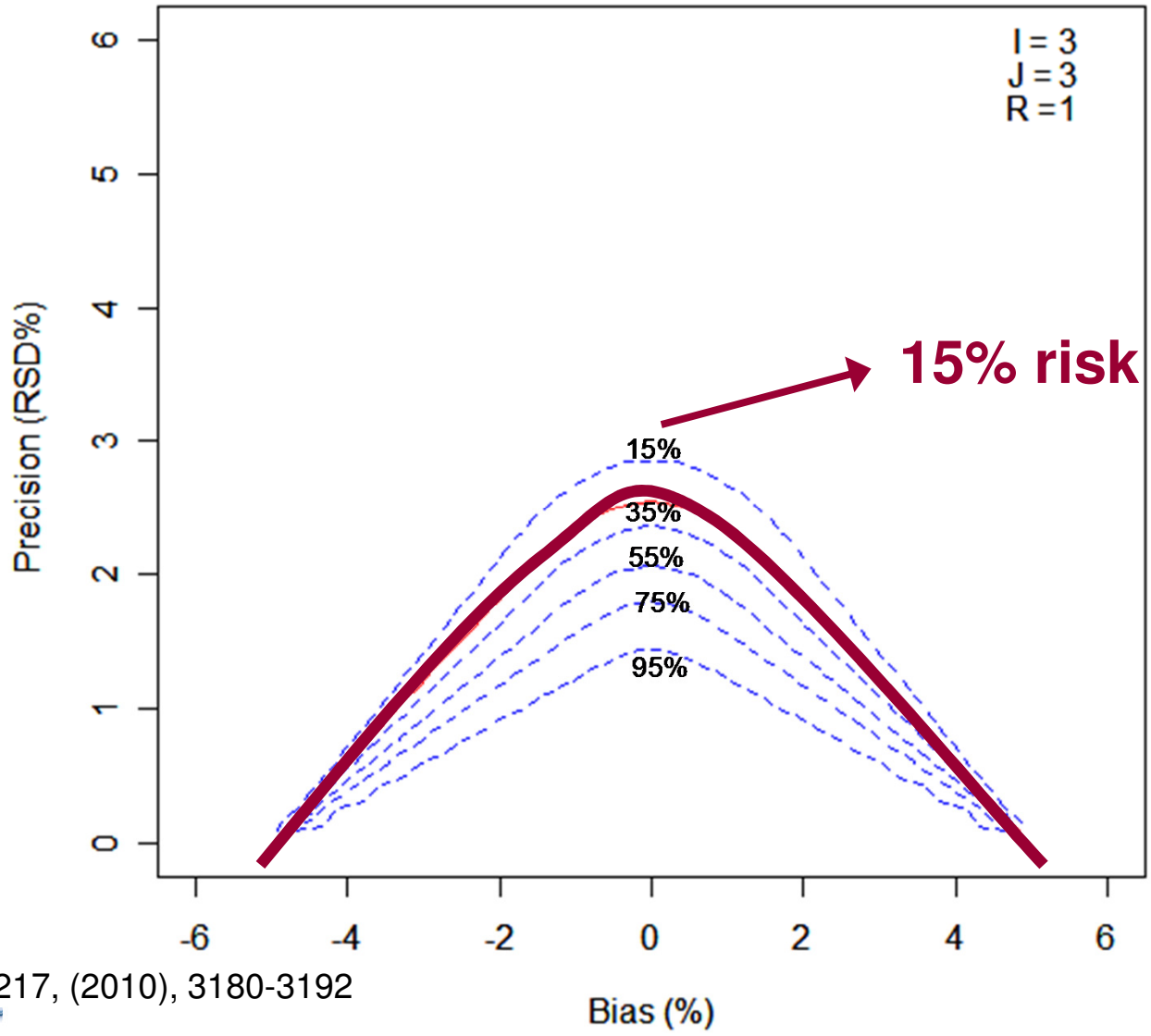
$\varepsilon_{ij} \sim iN(0, \sigma_\varepsilon^2)$,

$R = \sigma_\alpha^2 / \sigma_\varepsilon^2$

$\lambda_{Just} = \pm 2\%$

$\lambda_{Fid} = 3\%$

$\beta = 0.95$



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

Accuracy Profile

Validation experiments

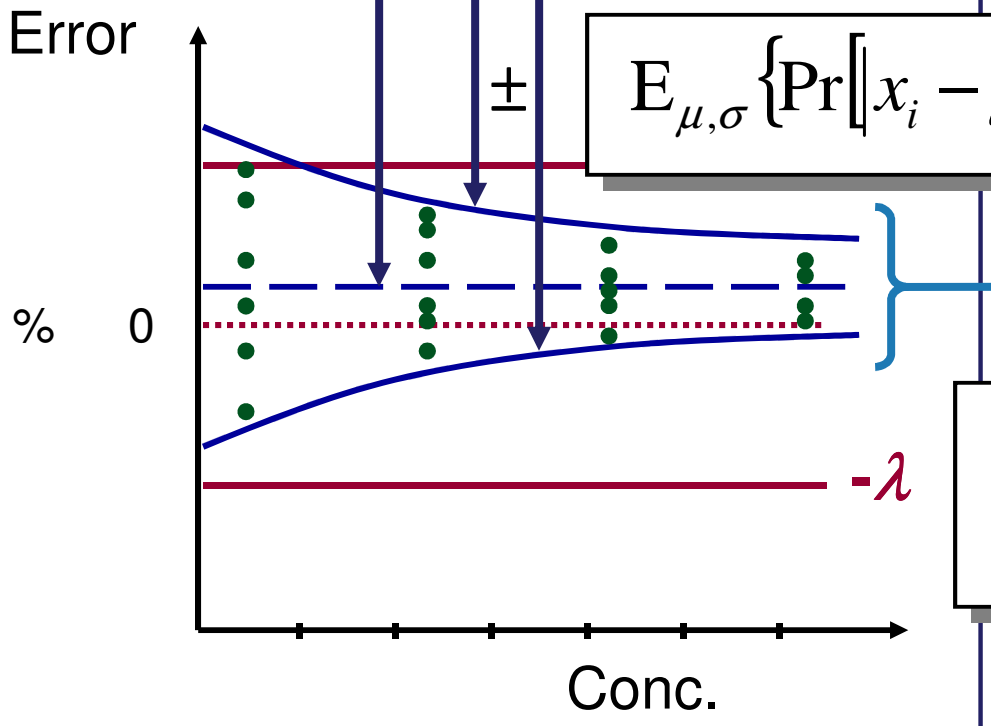
Bias

$$biais_j = \hat{\mu}_j - \bar{x}_{.j.}$$

Intermediate Precision

$$\hat{\sigma}^2_{W,j} + \hat{\sigma}^2_{B,j}$$

Total error



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

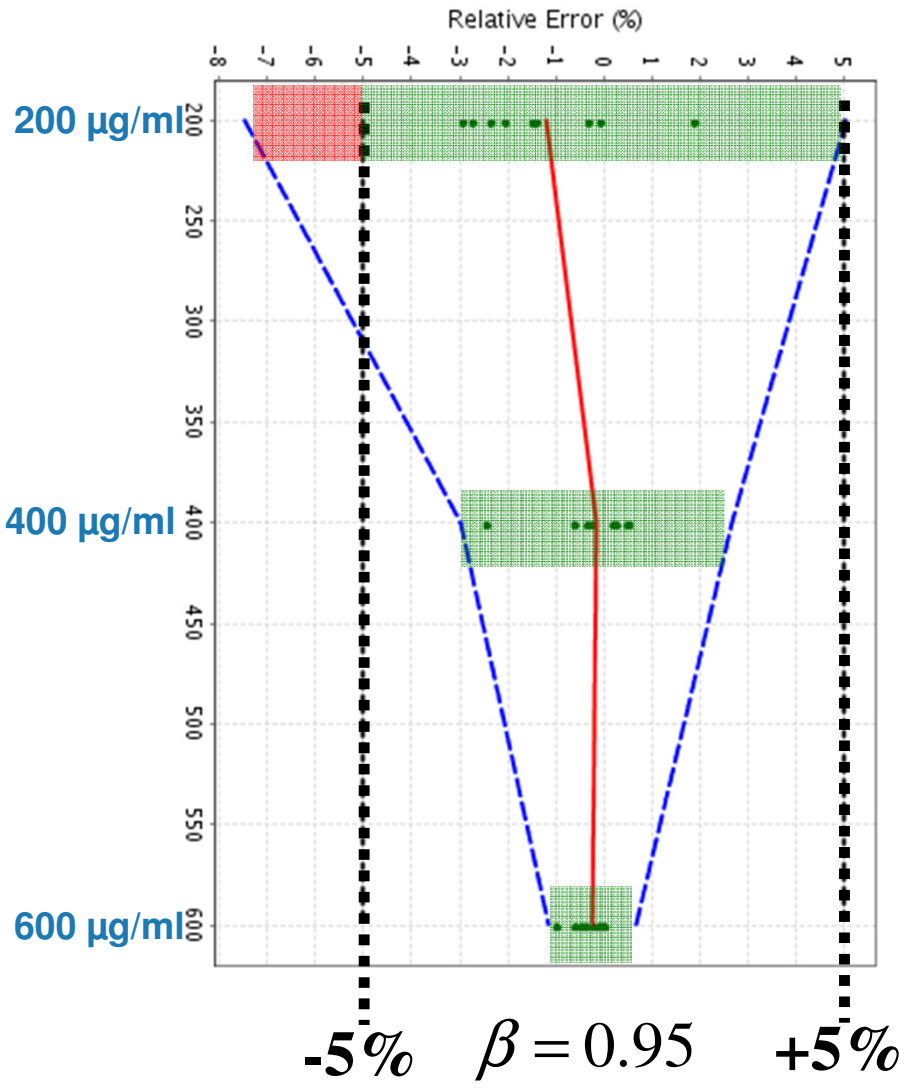
Predictive Interval with a known risk

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

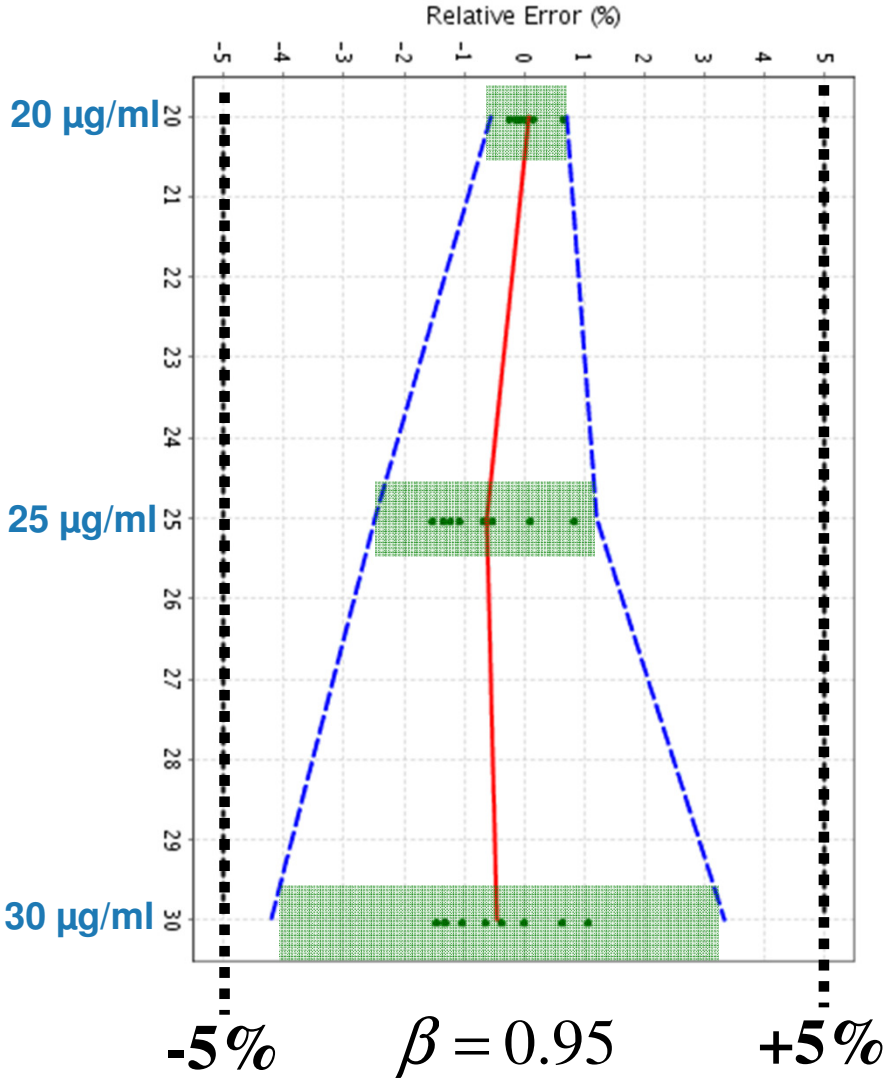
λ = acceptance limits of e.g. 5%

Example

Paracetamol

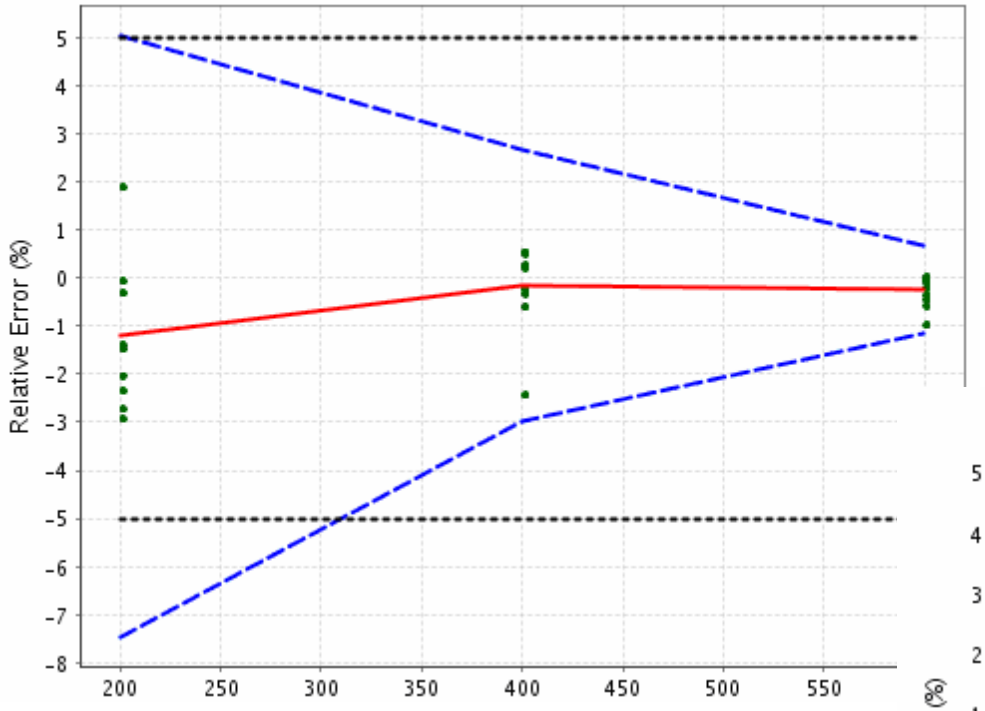


Codeine

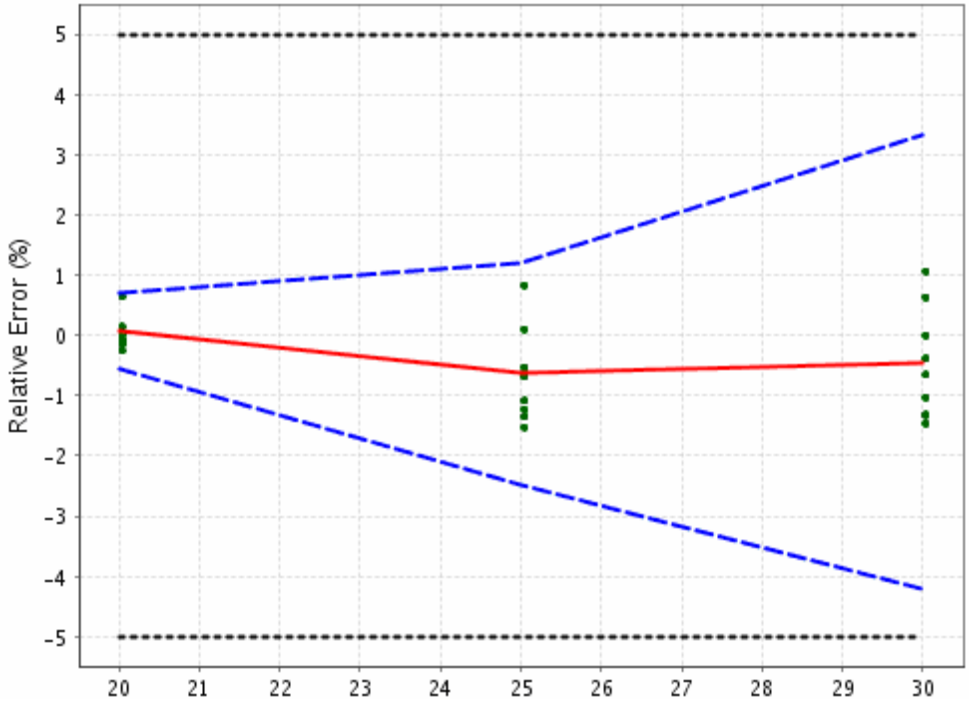


Example

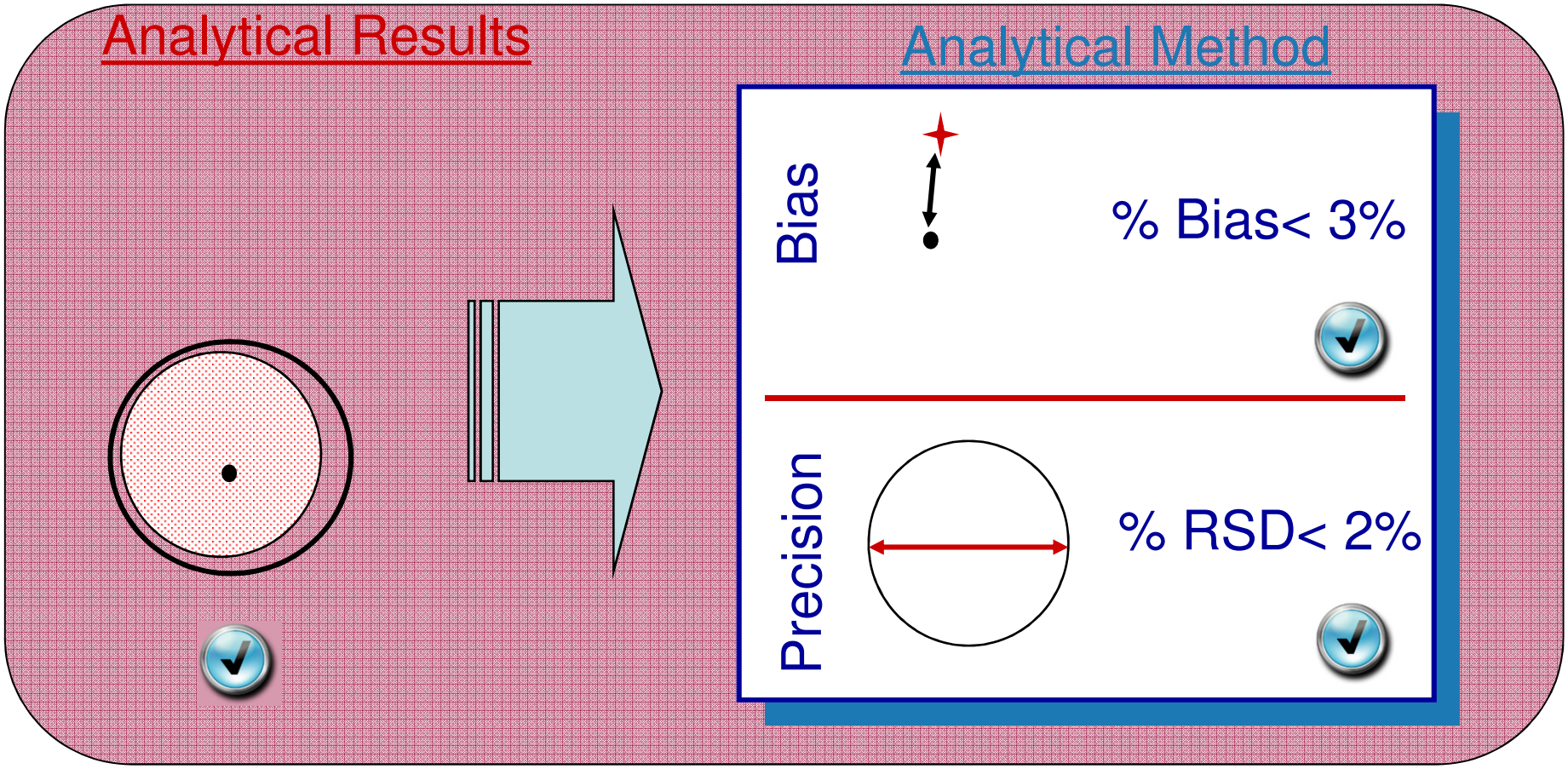
Paracetamol



Codeine



Analytical Method Validation



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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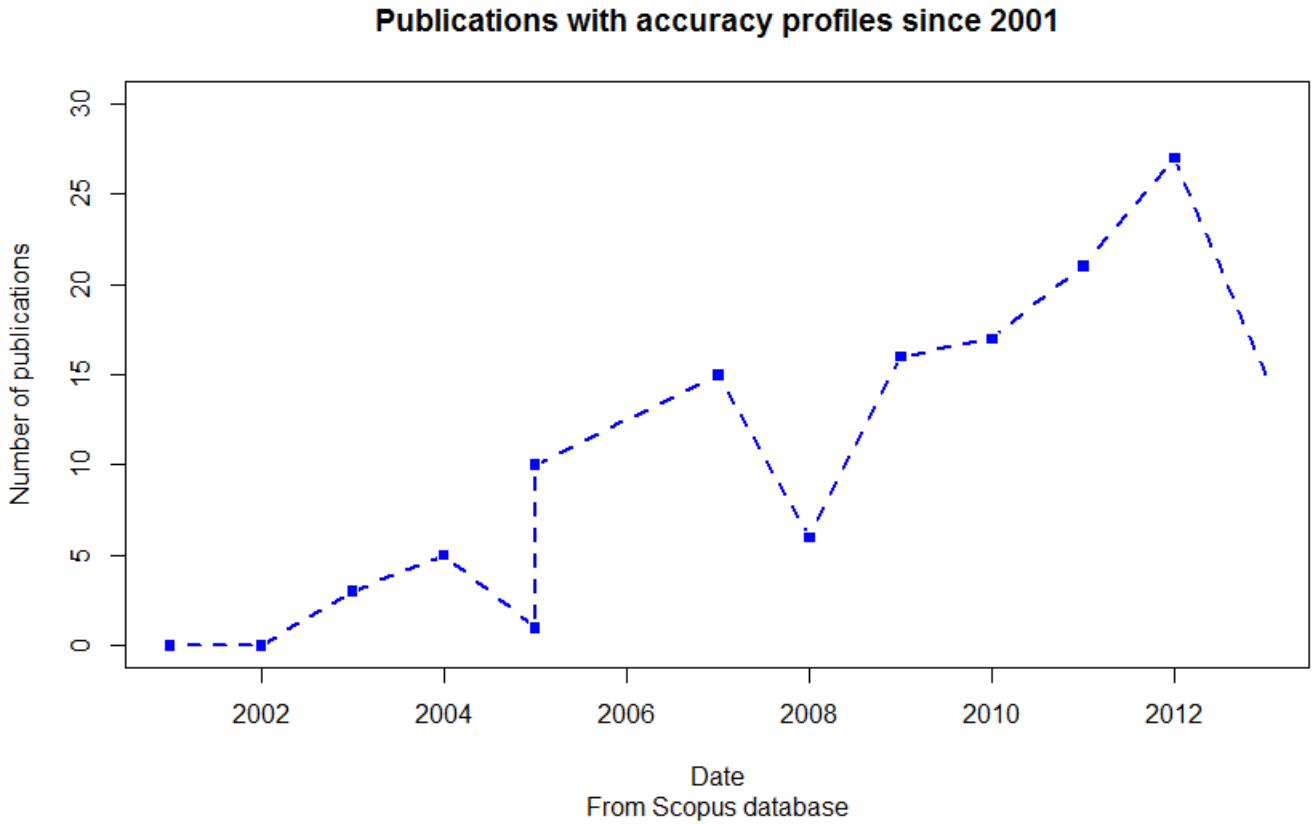
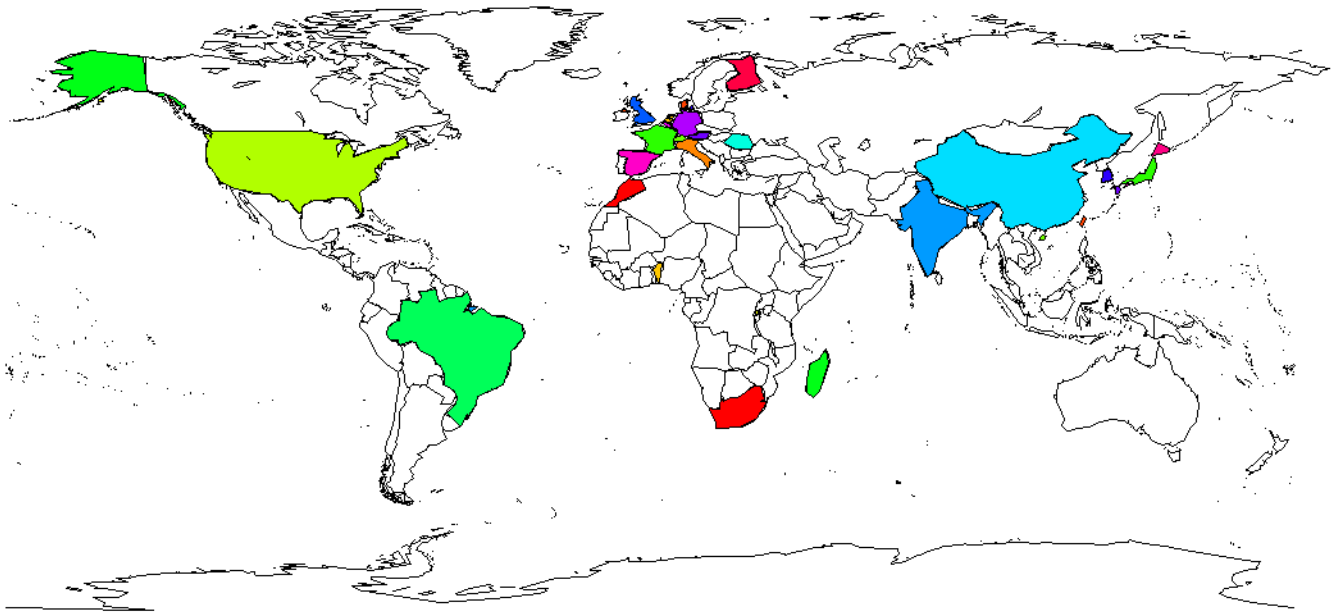
Use of accuracy profiles
e.noval & Seelva

136 publications



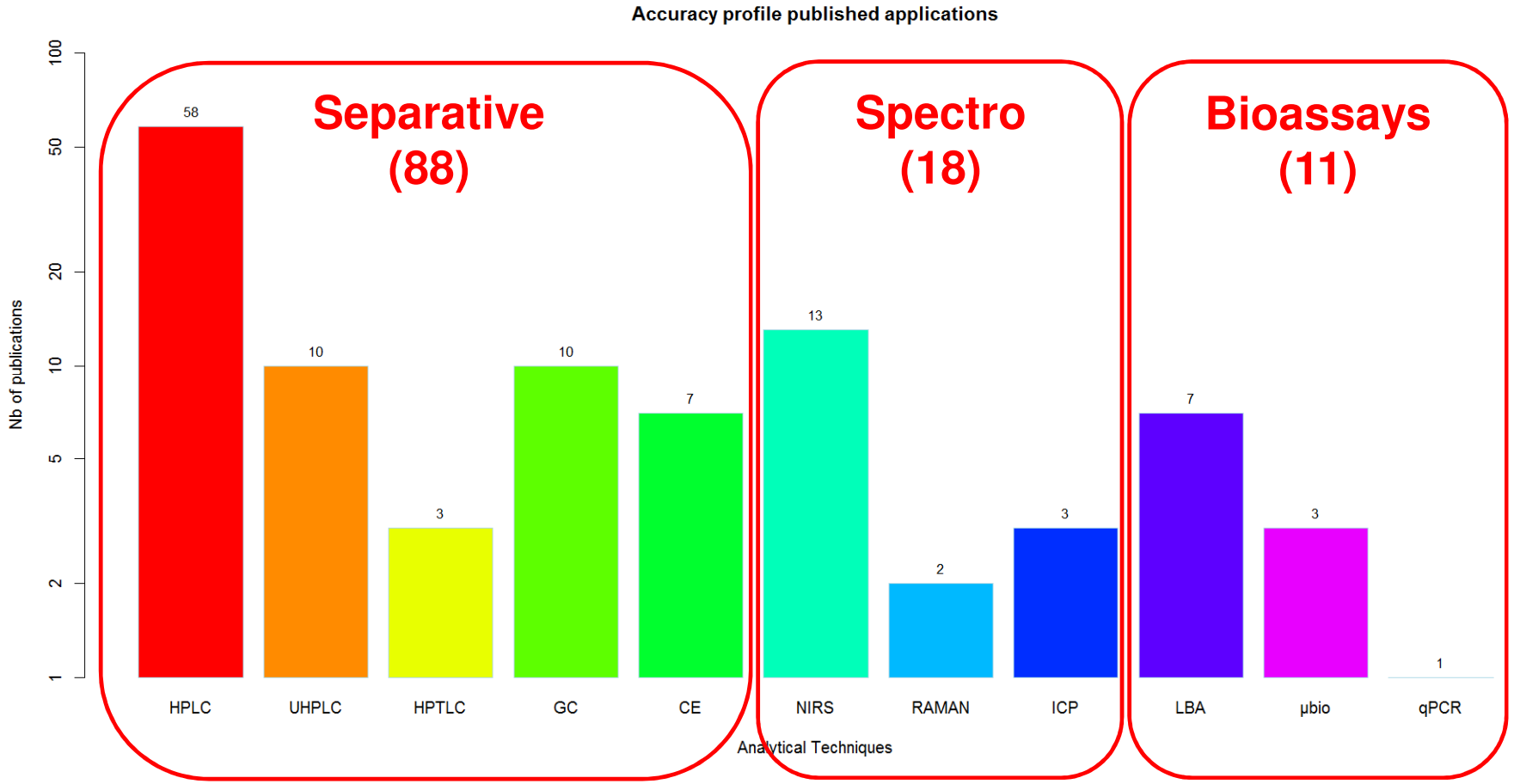
Use of accuracy profiles
e.noval & Seelva

- Countries using Accuracy profiles



Use of accuracy profiles e.noval & Seelva

- What analytical techniques:



Content

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

Future

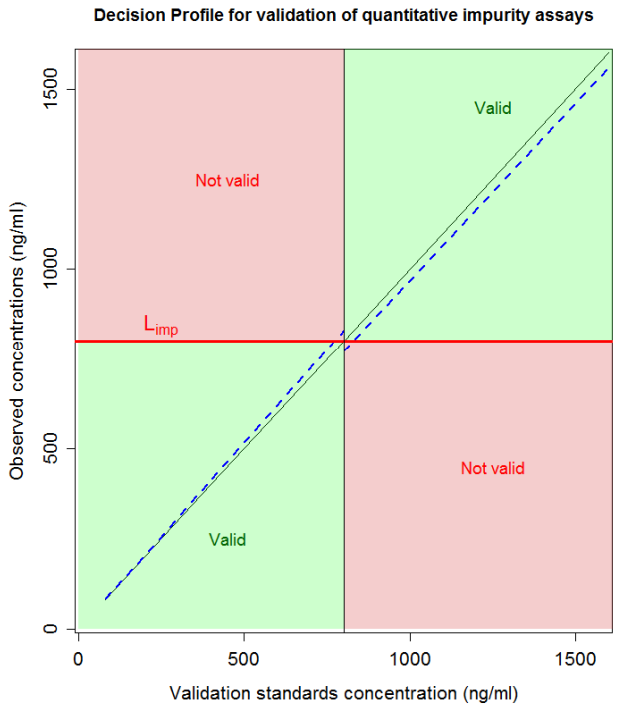
- **Switch** from the traditional check list validation & transfer to rewarding, useful and predictive approaches.

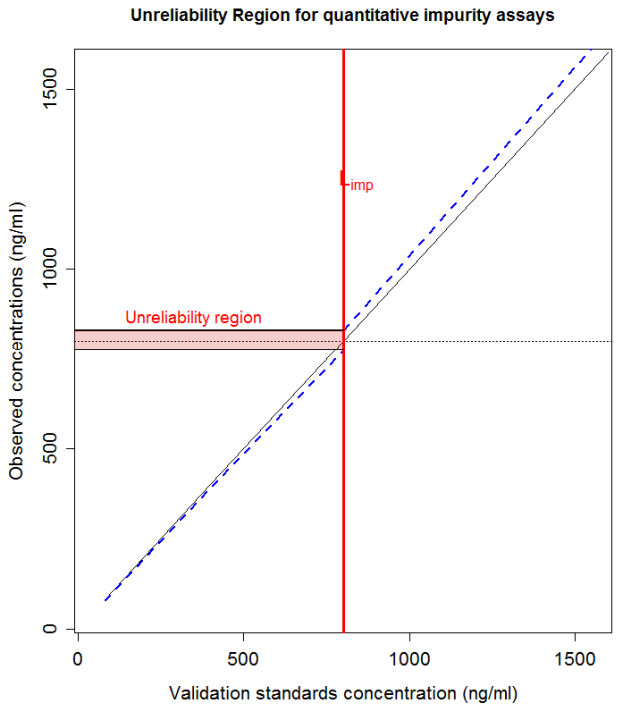
- Provide methodologies to declare methods valid or transferable by controlling the risks of erroneous decisions.

Future

- **Validating analytical methods for content assays and quantitative impurity assays:**

➔ making the correct decision about product compliance with respect to their specification limits.

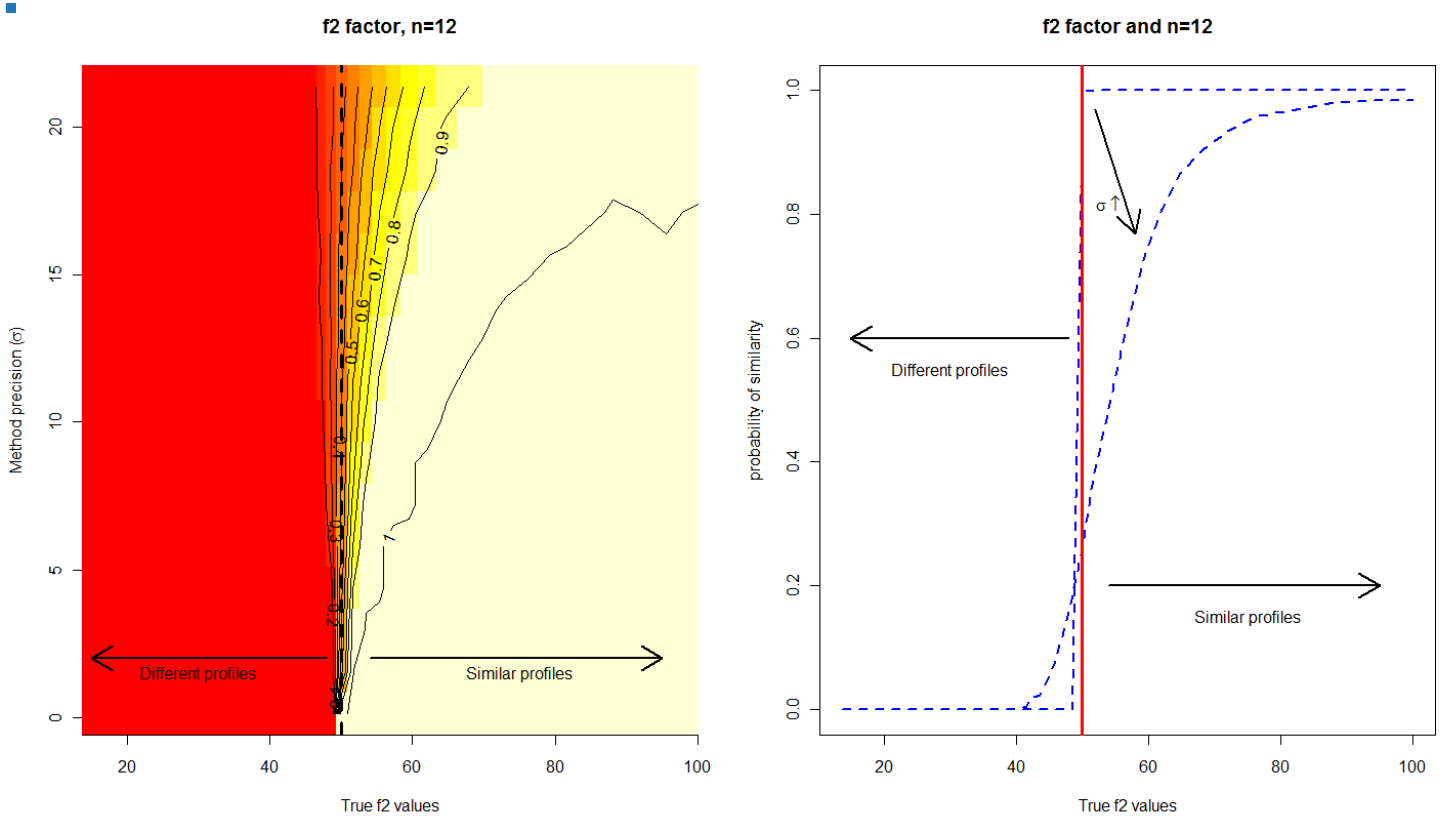




E. Rozet *et al.*, Quality by Design Compliant Analytical Method Validation, *Anal. Chem.* 2012, 84, 106–112

Future

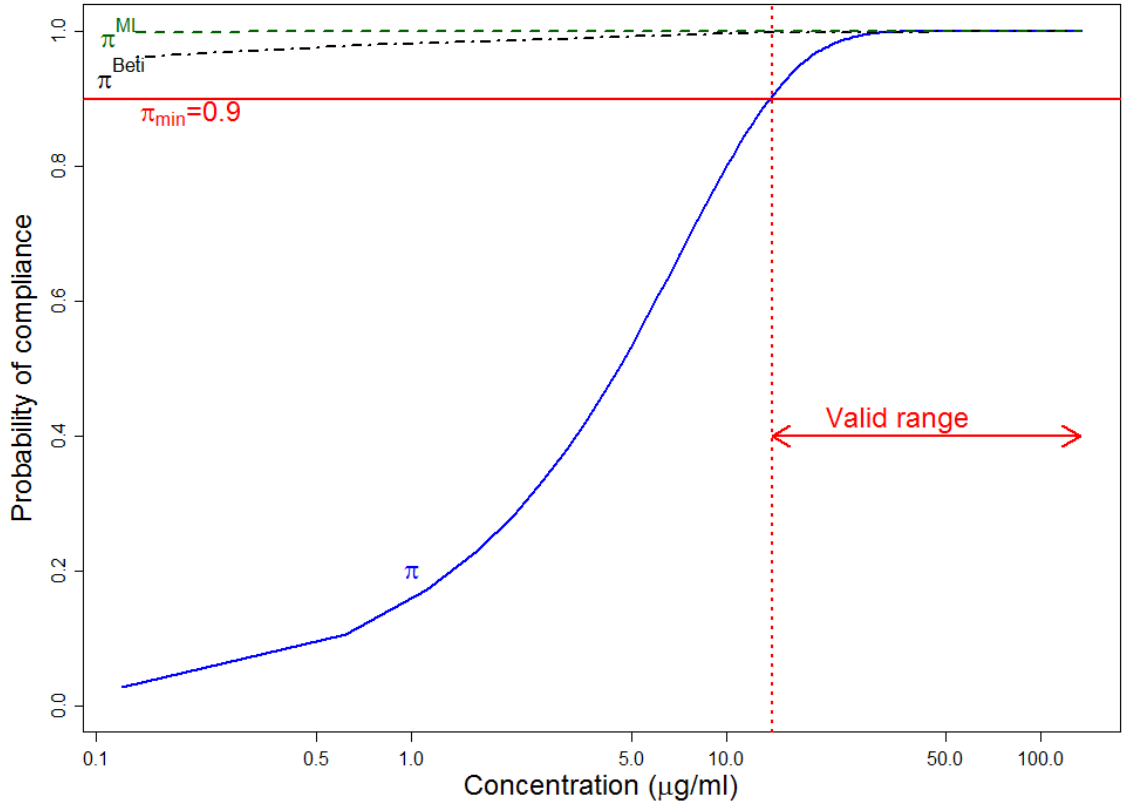
- **Validating analytical methods involved in dissolution assays.**



E. Rozet *et al.*, Validation of analytical methods involved in dissolution assays: Acceptance limits and decision methodologies, *Anal. Chim. Acta*, 751 (2012) 44.

Future

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

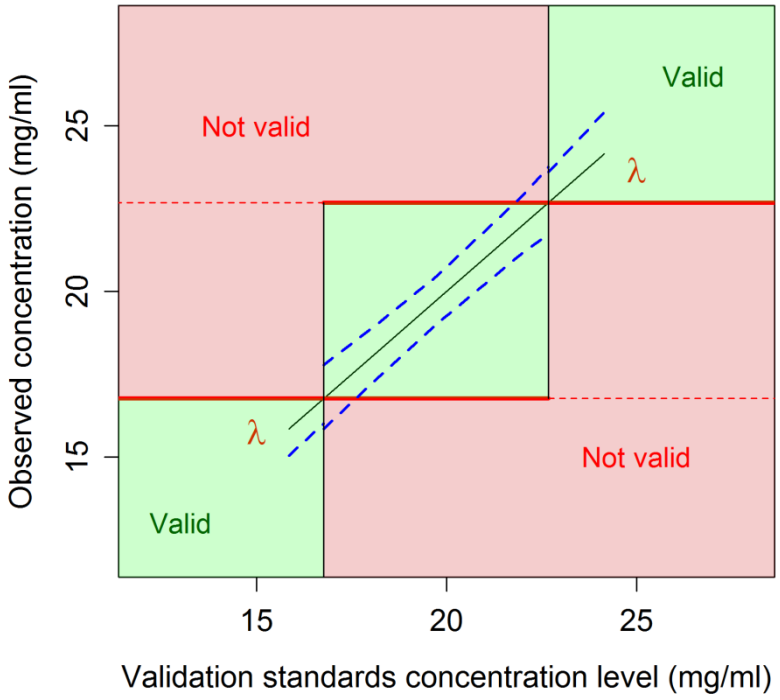


E. Rozet *et al.*, *Anal. Chim. Acta*, 705 (2011) 193– 206.

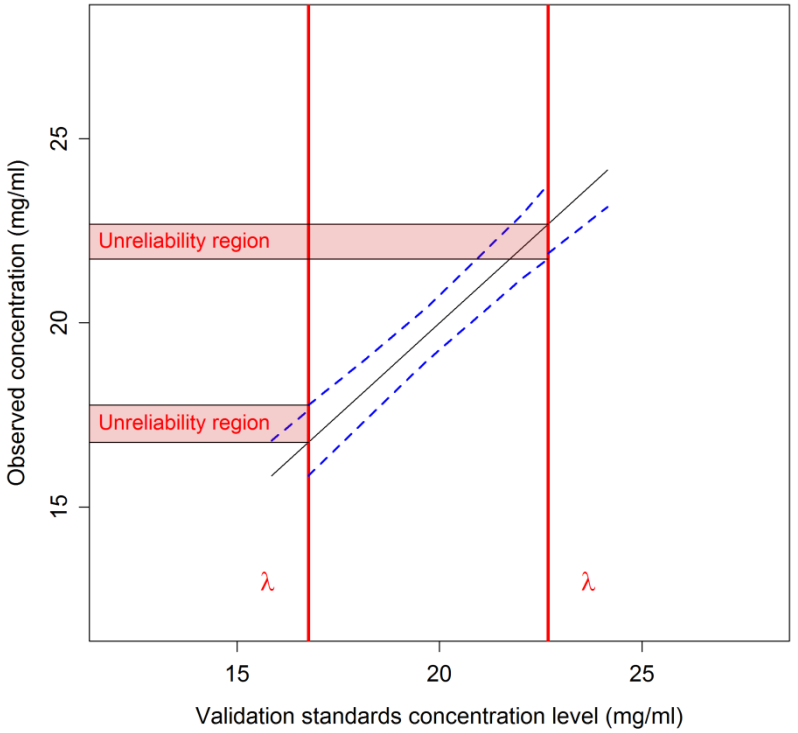
Future

- **Validating analytical methods for Uniformity of Dosage Units**

Decision profile



Unreliability regions



E. Rozet *et al.*, Methodology for the Validation of Analytical Methods involved in Uniformity of Dosage Units tests, *Anal. Chim. Acta*, 760 (2013) 752.

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 **β-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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