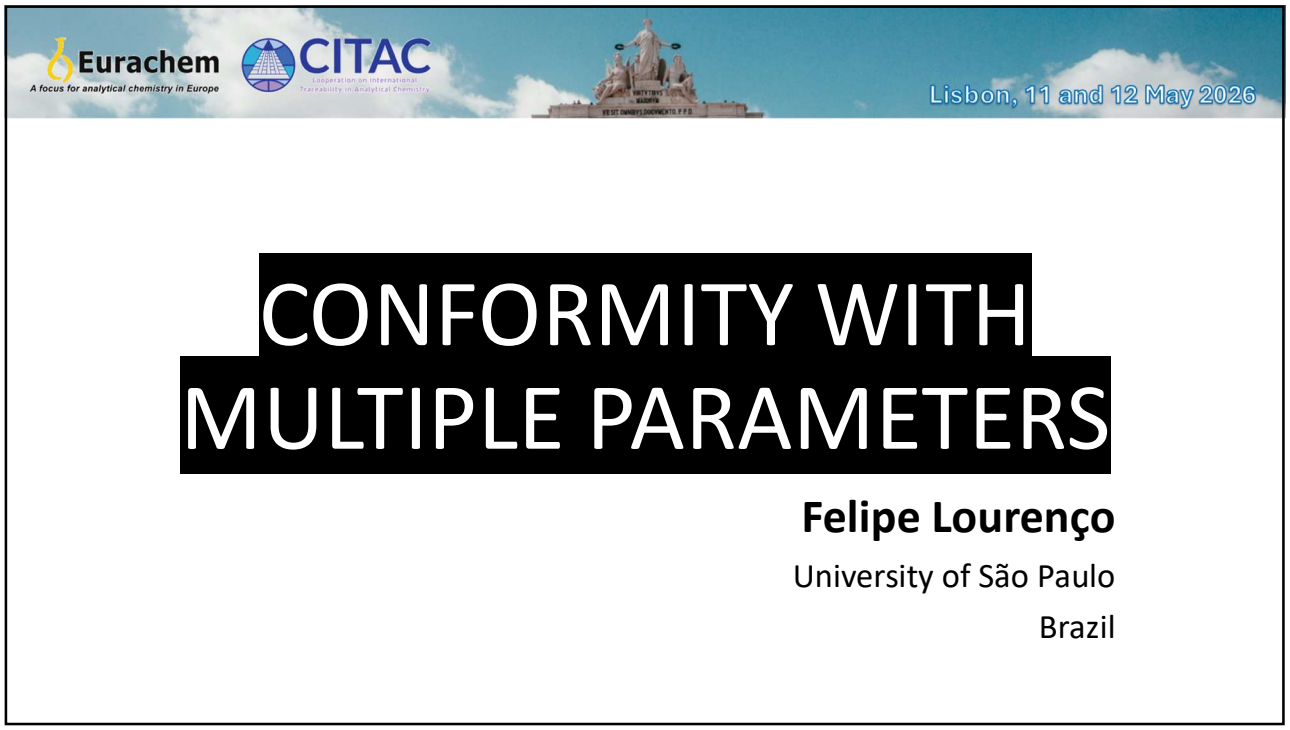

CONFORMITY WITH MULTIPLE PARAMETERS

Felipe Lourenço
University of São Paulo
Brazil

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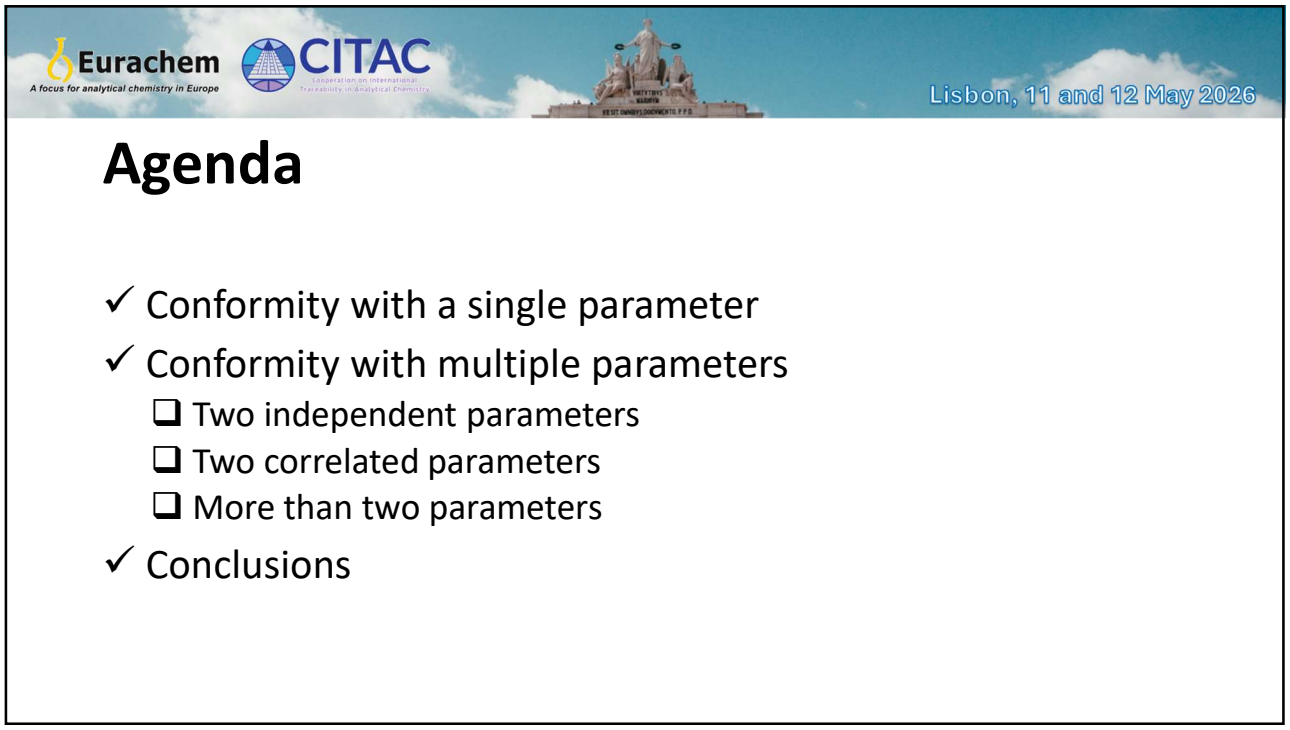

Agenda

- ✓ Conformity with a single parameter
- ✓ Conformity with multiple parameters
  - ❑ Two independent parameters
  - ❑ Two correlated parameters
  - ❑ More than two parameters
- ✓ Conclusions

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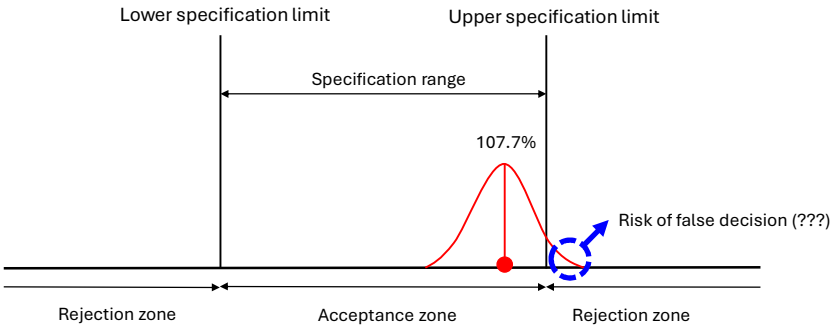
Conformity with a single parameter



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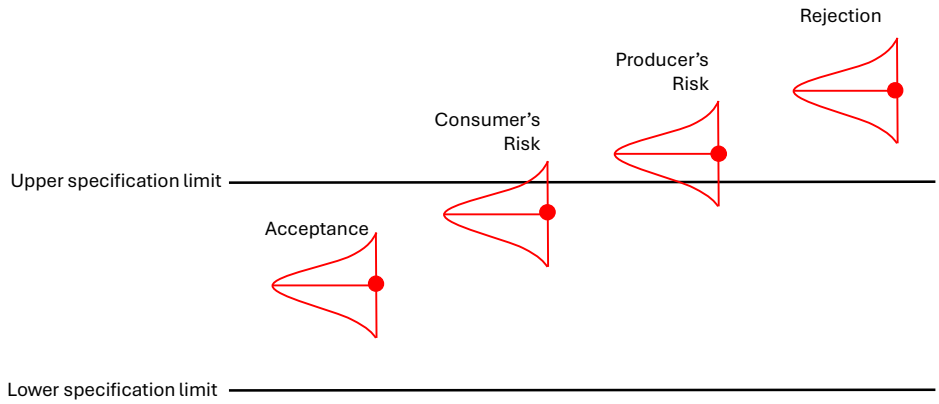
Use of Uncertainty Information...



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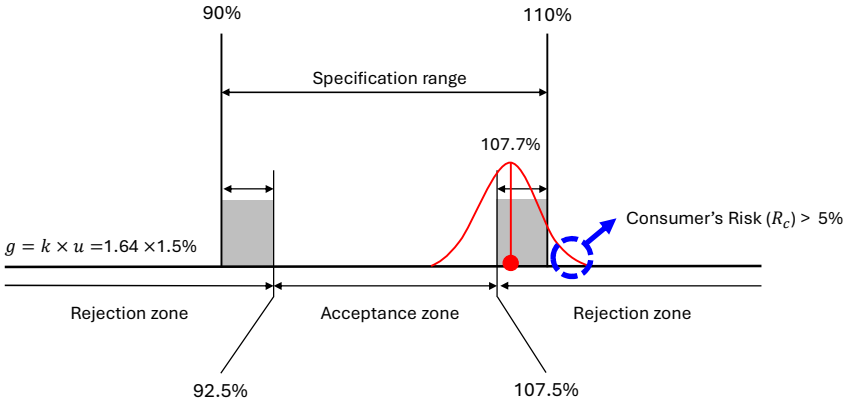
Decision rules with guard bands



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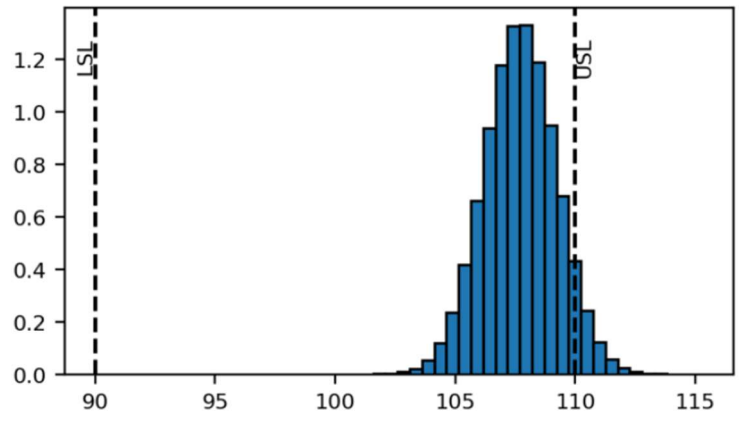
Particular consumer's risk...



Monte Carlo Method (MCM): STEP 1

Random generator (z_j)

z_j: "NORMSINV(RAND())"

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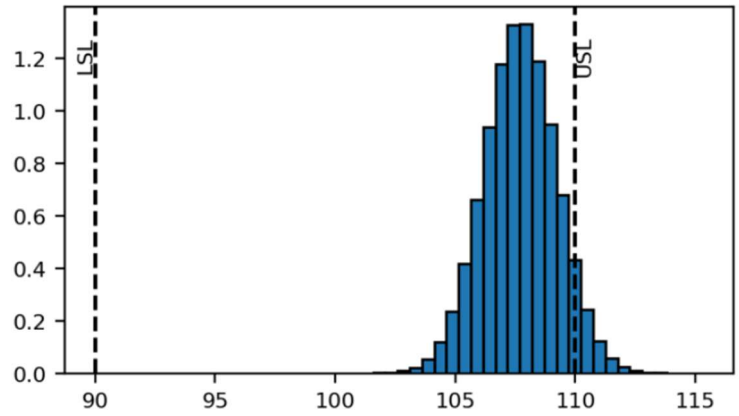
Particular consumer's risk...



Monte Carlo Method (MCM): STEP 2

Simulated values (x_j)

"=X+ z_j*u_X"

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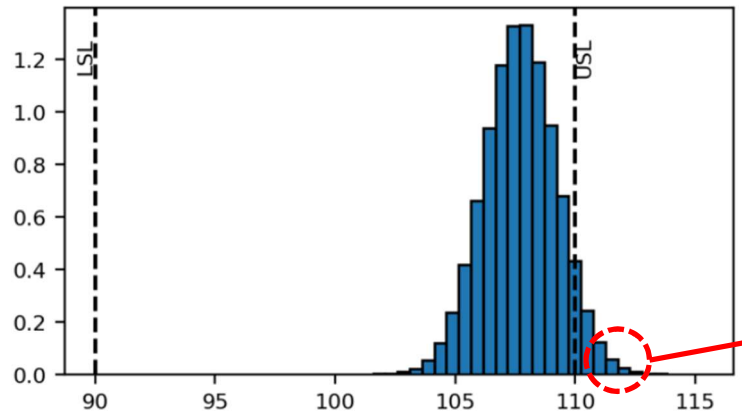
Particular consumer's risk...



Monte Carlo Method (MCM): STEP 3

If LSL $\leq x_j \leq$ USL: $c_j = 0$

Else: $c_j = 1$

$$R_c = \frac{\sum_j^m c_j}{m} = 6.3\%$$

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Conformity with multiple parameters

✓ In many cases, acceptance of a tested item or batch is based on multiple parameters

✓ Considering a medicines with 2 APIs:

- ❑ API 1: 107.4 ± 3.0% (Specification limits: 90-110%)
- ❑ API 2: 107.0 ± 3.0% (Specification limits: 90-110%)
- ❑ Assuming independent ($r_{12} = 0$) parameters

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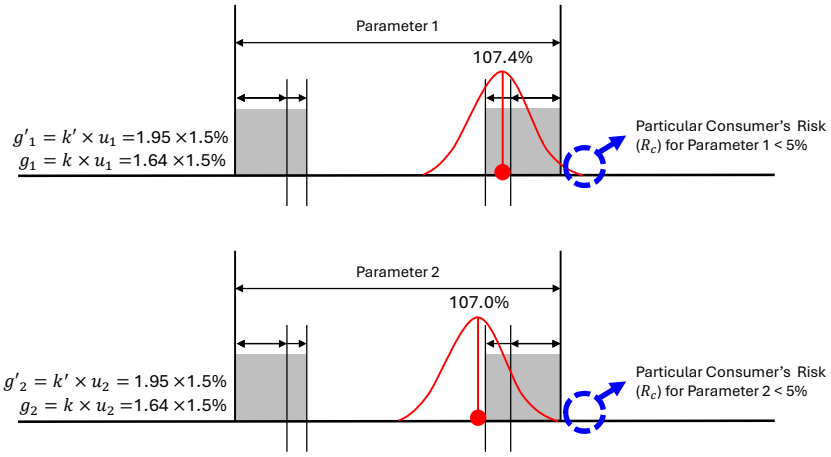
Conformity with multiple parameters



HOWEVER, total risk may be higher than 5%...

$$R_c^T = 1 - (1 - R_c)^n$$

n	R_c^T
2	**9.75%**
3	14.26%
4	18.55%
5	22.62%

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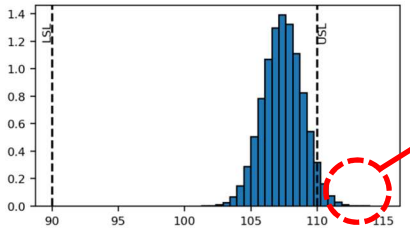
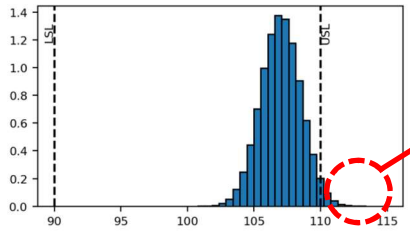
Two independent parameters...



R_{c_1} = 4.2%



R_{c_1} = 2.3%

Total risk will be...

$$R_c^T = R_{c_1} + R_{c_2} - P(1 \cap 2)$$

...for independent parameters:

$$P(1 \cap 2) = R_{c_1} \times R_{c_2}$$

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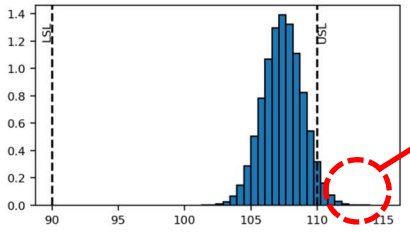
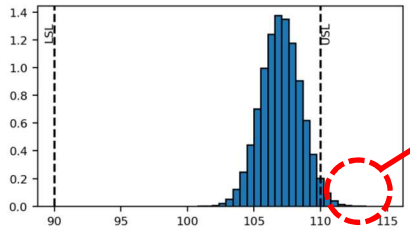
Two independent parameters...



R_{c_1} = 4.2%



R_{c_1} = 2.3%

Total risk will be...

$$R_c^T = 1 - \prod_i^n (1 - R_{c_i})$$

... for this case:

$$R_c^T = 1 - (1 - 0.042) \times (1 - 0.023)$$

$$R_c^T = 6.4\%$$

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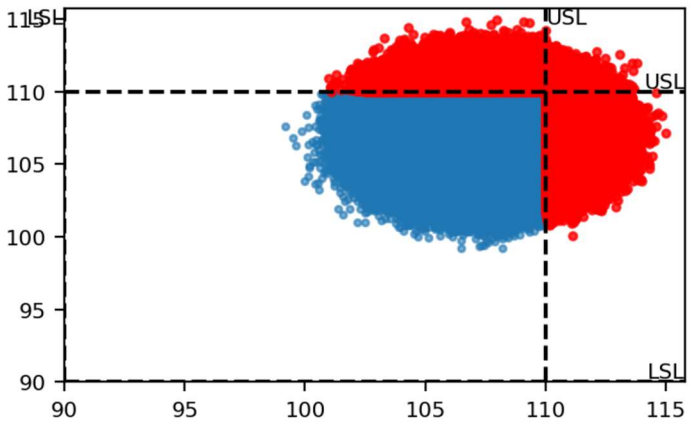
Two independent parameters...



Monte Carlo Method:
STEP 1

Random generators (z_{1_j} and z_{2_j})

z_{1_j}: "=NORMSINV(RAND())"
z_{2_j}: "=NORMSINV(RAND())"

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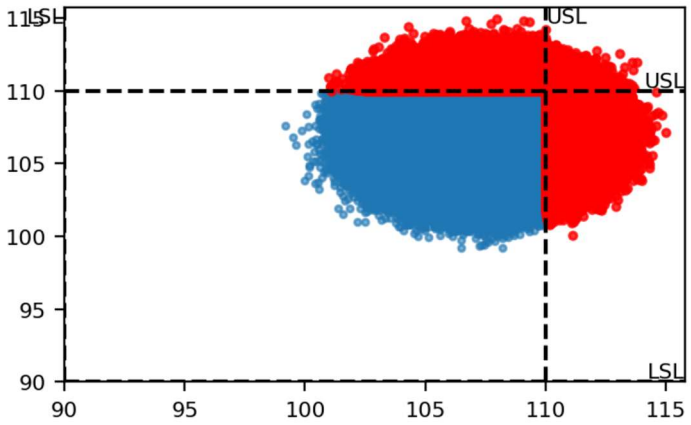
Two independent parameters...



Monte Carlo Method:
STEP 2

Simulated values (x_{1_j} and x_{2_j})

"=X_1+ z_{1_j}*u_{X_1}"
"=X_2+ z_{2_j}*u_{X_2}"

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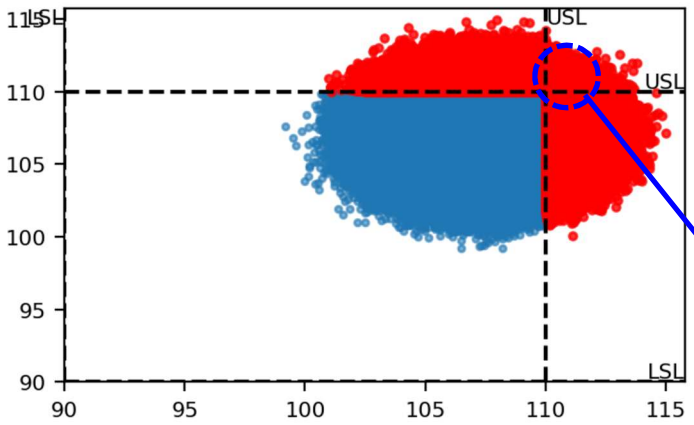
Two independent parameters...



Monte Carlo Method:
STEP 3

If $LSL_1 \leq x_{1_j} \leq USL_1$ and
$LSL_2 \leq x_{2_j} \leq USL_2$: $c_{T_j} = 0$
Else: $c_{T_j} = 1$

$$R_c^T = \frac{\sum_j^m c_{T_j}}{m} = 6.4\%$$

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Conformity with multiple parameters

- ✓ Parameters can be correlated due to:
  - ❑ intrinsic characteristics of the tested item or batch
  - ❑ the way the parameters are measured
- ✓ Considering a medicines with 2 APIs:
  - ❑ API 1: 107.4 ± 3.0% (Specification limits: 90-110%)
  - ❑ API 2: 107.0 ± 3.0% (Specification limits: 90-110%)
  - ❑ Assuming correlated ($r_{12} = 0.85$) parameters

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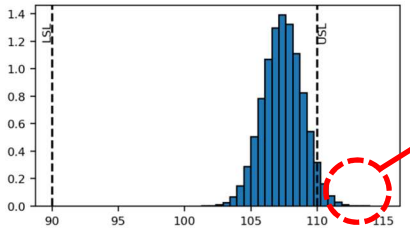
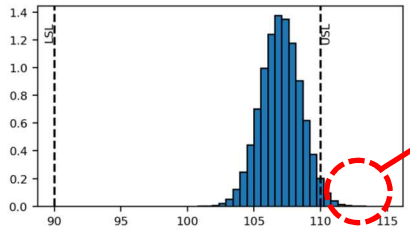
Two correlated parameters...



R_{c_1} = 4.2%



R_{c_1} = 2.3%

Particular risk values...

...will NOT be affect by correlation between parameters 1 and 2!

Total risk value...

...may be INSCREAED or DECREASED due to correlation!

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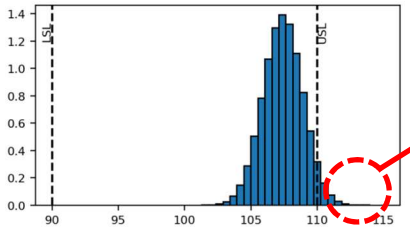
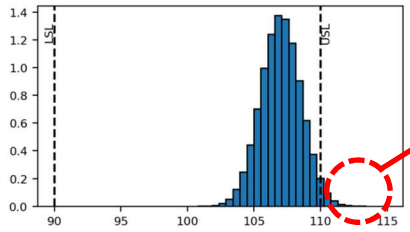
Two correlated parameters...



R_{c_1} = 4.2%



R_{c_1} = 2.3%

Total risk will be...

$$R_c^T = R_{c_1} + R_{c_2} - P(1 \cap 2)$$

...HOWEVER, for correlated parameters:

$$P(1 \cap 2) \neq R_{c_1} \times R_{c_2}$$

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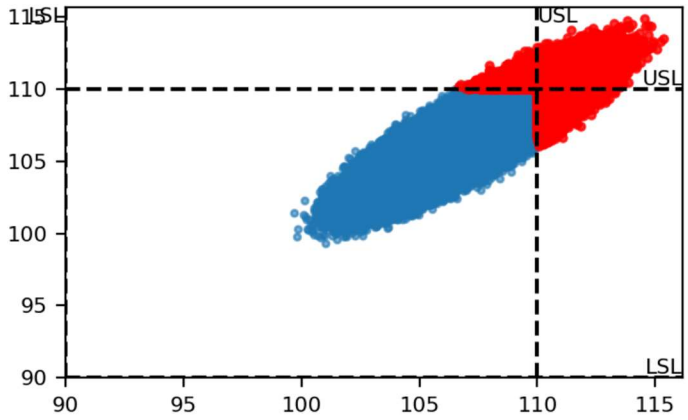
Two correlated parameters...



Monte Carlo Method:
STEP 1

Random generators (z_{1_j} and z_{2_j})

z_{1_j}: "=NORMSINV(RAND())"
z_{2_j}: "=NORMSINV(RAND())"

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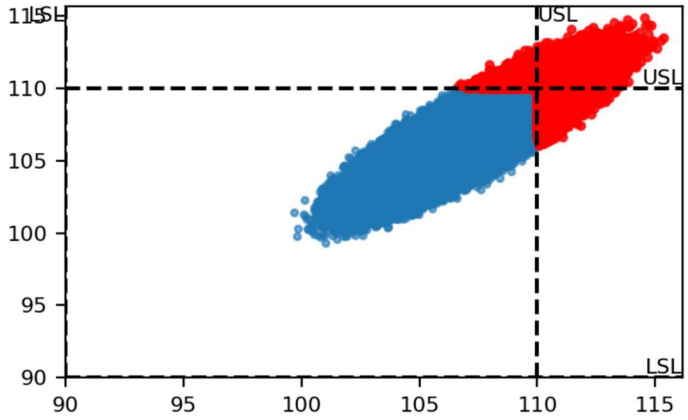
Two correlated parameters...



Monte Carlo Method:
STEP 2

Simulated values (x_{1_j} and x_{2_j}) using Cholesky decomposition

"$=X_1 + z_{1_j} * u_{X_1}$"
"$=X_2 + (z_{1_j} r_{12} + z_{2_j}\sqrt{1 - r_{12}^2}) * u_{X_2}$"

r_{12} is the correlation between parameters 1 and 2

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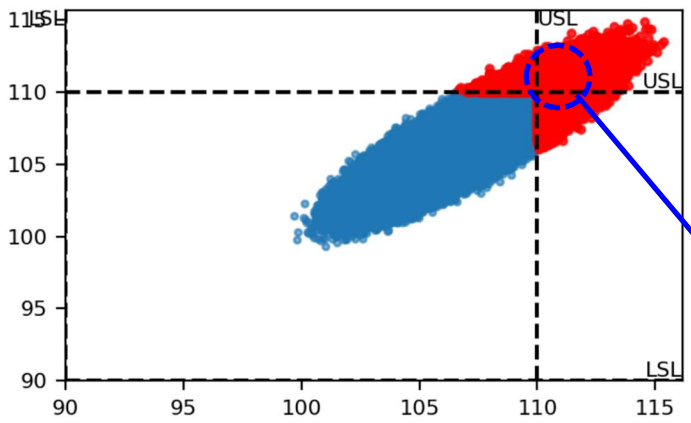
Two correlated parameters...



Monte Carlo Method:
STEP 3

If $LSL_1 \leq x_{1_j} \leq USL_1$ and
$LSL_2 \leq x_{2_j} \leq USL_2$: $c_{T_j} = 0$
Else: $c_{T_j} = 1$

$$R_c^T = \frac{\sum_j^m c_{T_j}}{m} = 4.9\%$$

Conformity with multiple parameters

✓ Conformity with more than two parameters

✓ Considering a medicine with 3 APIs:
- ❑ API 1: 95 ± 4 mg/tablet (Specification limits: 90-110 mg/tablet)
- ❑ API 2: 46 ± 2 mg/tablet (Specification limits: 45-55 mg/tablet)
- ❑ API 3: 185 ± 6 mg/tablet (Specification limits: 180-220 mg/tablet)
- ❑ Correlation matrix: $r_{12} = 0.8$, $r_{13} = 0$, and $r_{23} = 0$

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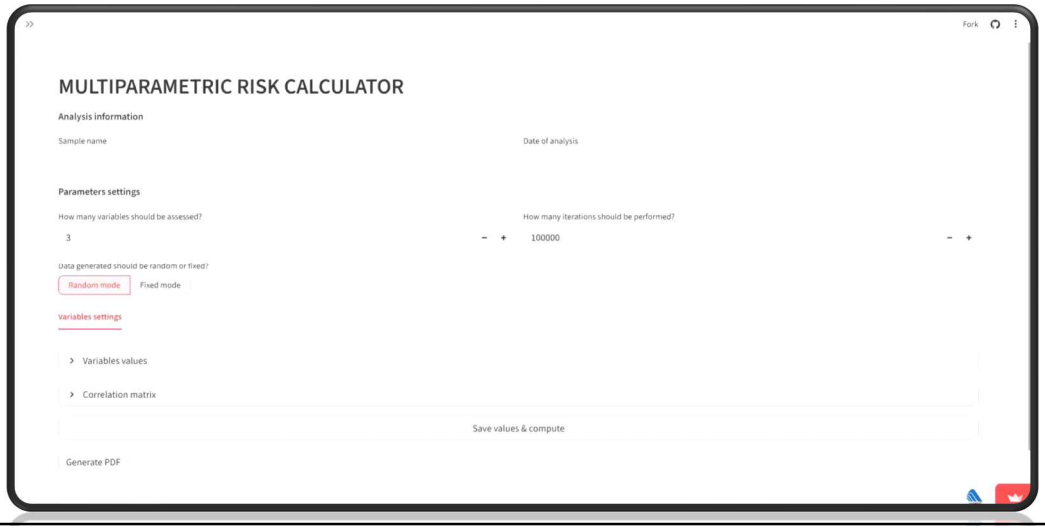
Conformity with multiple parameters



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Conclusions!

In practice, we rarely measure a single parameter. When multiple parameters are involved, the decision problem becomes inherently multivariate. Ignoring this can lead to unreliable risk estimation. That is why conformity assessment must move from a univariate to a multivariate perspective.

“More parameters, more chances to be wrong!”

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References

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- **WILLIAMS & MAGNUSSON.** Eurachem/CITAC Guide: Use of uncertainty information in compliance assessment. 2021.

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