Analytical Risk Assessment from Validation results

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Purpose: During method validation, setting Acceptance Criteria should be directly linked to the Intended Use of the method and to the specifications of the product to be analyzed.
This poster proposes Operating Characteristic Curves, a graphical tool based upon an Analytical Risk Assessment, to evaluate the performance of a method regarding the risk of getting false-negative results during its routine use.
Methods: Several scenarios are analyzed : Assay of a Drug Substance with 98.0-102.0 % specifications, Assay of active substance in Drug Product with 95.0-105.0 % specifications, Assay of preservative in Drug Product with 90.0-110.0 % specifications, Elisa testing with QC samples to meet 85.0-115.0 % specifications
For each scenario, Operating Characteristic Curves were determined with Excel Solver using the following formula: Result = NORMDIST(USL, BIAS, RSD,TRUE) - NORMDIST(LSL, BIAS, RSD,TRUE)
With USL and LSL = Upper and Lower Specification Levels, BIAS = Systematic Bias percentage estimated during Accuracy step of method validation, RSD= Repeatability Relative Standard Deviation estimated during validation, TRUE= logical operator
The corresponding Result is the probability to get an individual data within the specifications for a sample with an actual content at 100.0%, and (1-Result) is then the Risk to obtain a false-negative result.
Setting levels of Risk from low (0.01%) to unacceptable values (20%) allowed to draw the relationship between SD and BIAS to reach the chosen Risk value. For each Risk value, an Operating Characteristic curve is obtained, with MEAN values on the X-axis and SD values on the Y-axis. Gathering all these curves in a same graph provides a graphical tool that defines zones of acceptable (and unacceptable) risks.

Results: Operating Characteristic Curves (OCC) of two scenarios (+/- 5% specifications and +/-15% limits) are provided in Figures 2 and 4. For example, a method with 1.0% Bias and 3.0% RSD (Method 2), the Risk of generating a false-negative result for a batch with an actual content at 100.0% would depend on your specification limits: far above 20% for 98-102% specifications (gets out of figure 1), between 10 and 20% for 95-105% specifications (Figure 2), close to 0.1% for 90-110% specifications (Figure 3), below 0.01% for 85-115% specifications (Figure 4). Other examples are tabulated under the graphs for each scenario.
Conclusions: The Operating Characteristic Curves are useful graphical tools for development analysts, in order to check if their methods will be capable enough to generate reliable data, and for QC analysts to provide sound scientific argumentation regarding results obtained out of the predefined limits.
As the risks you can accept may decrease during the development of your product, the same graph can be used as an evolving tool of method performance evaluation during its life cycle management.

PURPOSE & OBJECTIVES

Prior to method validation, Acceptance Criteria are set according to the Intended Use of the method and to the specifications of the product to be analyzed.
In the Pharmaceutical Industry, descriptive acceptance criteria are commonly used.
After the Validation exercise, performed according to ICH Q2 (R1) guideline[1], the method is considered as valid if predefined the acceptance criteria are met.

But additional interpretation efforts are necessary in order to evaluate more precisely the real performances of the method.

This poster proposes Operating Characteristic Curves (OCC)[2], a graphical tool based upon an Analytical Risk Assessment, to evaluate easily the performance of an Assay method regarding the risk of getting "false-negative results" during its routine use. A false negative result is an OOS result obtained when the batch is actually within the specifications
Several curves are proposed in order to adapt the risk analysis to different specification limits.

METHODS

Four scenarios / Specification sets are proposed:

Intended Use	Specifications
Drug Substance	[98.0, 102.0%]
API in Drug Product	[95.0, 105.0%]
Preservative in DP	[90.0, 110.0%]
Elisa QC samples	[85.0, 115.0%]

For each scenario, OCC were determined with Excel Solver using the following formula:

RESULT = NORMDIST(USL, BIAS, RSD,TRUE) - NORMDIST(LSL, BIAS, RSD,TRUE)
USL & LSL = Upper and Lower Specification Limits
BIAS = Systematic Bias percentage *estimated during Accuracy step of method validation*[1],
RSD= Repeatability Relative Standard Deviation *estimated during Precision step of validation*[1]
TRUE= logical operator

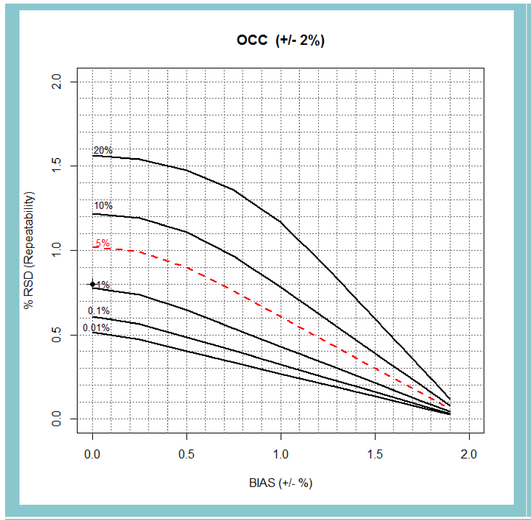
RESULT is the probability to get an individual data within the specifications for a "perfect sample" with an actual content at 100.0%
(1-RESULT) = Risk to obtain a false-negative result.

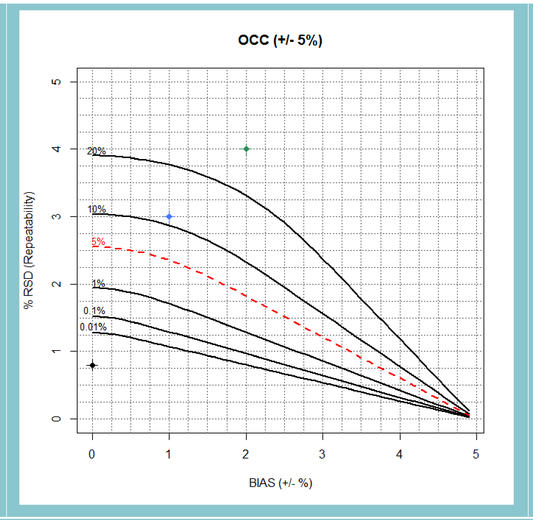
Risk levels are set from low (0.01%) to unacceptable values (20%), and 5 methods with different performances (see table below) are spotted at their corresponding calculated risk level.

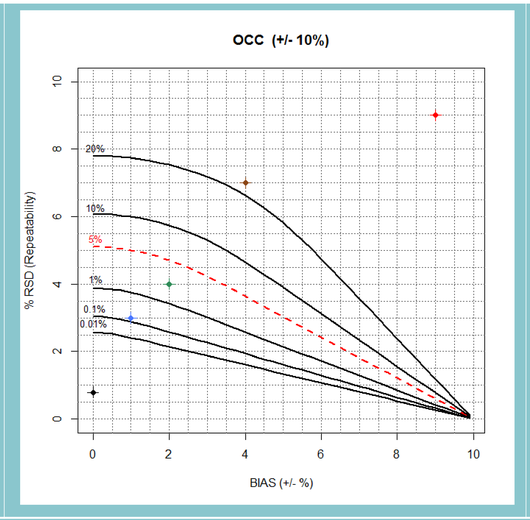
Method	BIAS	RSD
Method 1	0.0	0.8
Method 2	1.0	3.0
Method 3	2.0	4.0
Method 4	4.0	7.0
Method 5	9.0	9.0

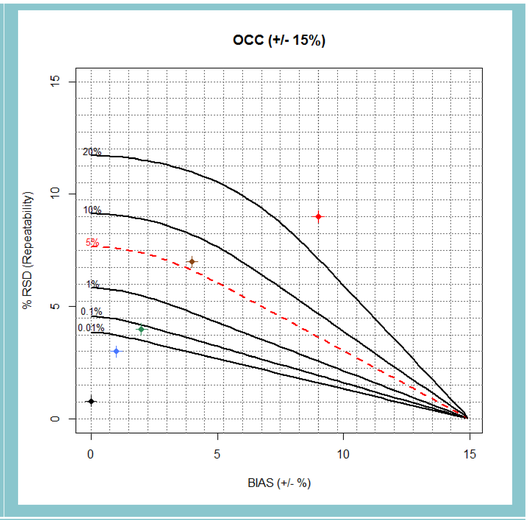
RESULTS

Operating Characteristic Curves (OCC) of the 4 scenarios are presented in Figures 1 to 4. Methods 1 to 5, with their various performance parameters (see Table 1), are plotted in each OCC Figure (when validation parameters do fit into the corresponding scale). Each plot can be situated between risk level curves, in order to evaluate the risk of generating false-negative results. Corresponding risks are summarized in Table 1.









FIGURES 1 to 4 : Assessment of risk levels of having an analytical data out of acceptance limits for a sample at 100.0%, according to method performances in terms of systematic bias (BIAS) and Precision (RSD).
The dotted line corresponds to the classical admissible 5%-risk level. The five (5) methods described in Table 1 are plotted with respect to the color code

FIGURE 1: Acceptance limits = [98.0, 102.0%], classical limits for Drug Substance Assay

METHOD	BIAS	RSD	Risk of false-negative result (%)
Method 1	0.0	0.8	1%<Risk<5%
Method 2	1.0	3.0	Risk >>20%
Method 3	2.0	4.0	Risk >>20%
Method 4	4.0	7.0	Risk >>20%
Method 5	9.0	9.0	Risk >>20%

FIGURE 2: Acceptance limits = [95.0, 105.0%], classical limits for Assay of Active Substance in Drug Product

METHOD	BIAS	RSD	Risk of false-negative result (%)
Method 1	0.0	0.8	Risk<0.01%
Method 2	1.0	3.0	10%< Risk <20%
Method 3	2.0	4.0	Risk >20%
Method 4	4.0	7.0	Risk >>20%
Method 5	9.0	9.0	Risk >>20%

FIGURE 3: Acceptance limits = [90.0, 110.0%], classical limits for Preservative Assay

METHOD	BIAS	RSD	Risk of false-negative result (%)
Method 1	0.0	0.8	Risk <0.01%
Method 2	1.0	3.0	0.1%< Risk <1%
Method 3	2.0	4.0	1%< Risk <5%
Method 4	4.0	7.0	Risk >20%
Method 5	9.0	9.0	Risk >>20%

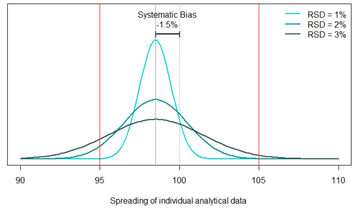
FIGURE 4: Acceptance limits = [85.0, 115.0%], classical limits during ELISA testing for QC samples

METHOD	BIAS	RSD	Risk of false-negative result (%)
Method 1	0.0	0.8	Risk <0.01%
Method 2	1.0	3.0	Risk <0.01%
Method 3	2.0	4.0	0.1%< Risk <1%
Method 4	4.0	7.0	5%< Risk <10%
Method 5	9.0	9.0	Risk >20%

Appendix: What is a false-negative result?

When one performs an analysis on a sample, only estimation of the actual content of the compound of interest is obtained. This estimation is more or less reliable, according to method performances.
The major indicators for method performances are
- systematic bias: for a mean Accuracy at 98.5%, systematic bias = 1.5% (the same for a mean Accuracy at 101.5%)
- Precision RSD

Extreme results for a "perfect batch" can get out of your acceptance criteria ([95.0; 105.0] in Figure 5), especially for high RSD values. This leads to a "False-negative result", as the batch will not be considered as compliant when its actual content is 100.0%.
Figure 5 : Spreading of analytical data for several analysis of a same "perfect batch" with an actual content at 100.0% when the method has a 98.5% Accuracy and 1%, 2% or 3% RSD.



CONCLUSIONS

The Operating Characteristic Curves OCC are useful graphical tools for development analysts, in order to check if their methods will be capable enough to generate reliable data.
Transfer of Knowledge about method performances between R&D and QC laboratories should allow the QC analysts and QC Managers to provide sound scientific argumentation regarding results obtained out of the predefined limits.
As the risks you can accept may decrease during the development of your product, the same graph can also be used as an evolving tool for method performance evaluation during its life cycle management.

REFERENCES

1. ICH Q2(R1) guideline. Available at: http://www.ich.org/
2. Small Molecules Collaborative Group and USPC Staff. Pharm Forum.35(3) (2009) 765–771.