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Analytical method transfer: New descriptive approach for acceptance criteria definition

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Abstract

Within the pharmaceutical industry, method transfers are now commonplace during the life cycle of an analytical method. Setting acceptance criteria for analytical transfers is, however, much more difficult than usually described. Criteria which are too wide may lead to the acceptance of a laboratory providing non-equivalent results, resulting in bad release/reject decisions for pharmaceutical products (a consumer risk). On the contrary, criteria which are too tight may lead to the rejection of an equivalent laboratory, resulting in time costs and delay in the transfer process (an industrial risk). The consumer risk has to be controlled first.

But the risk does depend on the method capability (tolerance to method precision ratio).

Analytical transfers were simulated for different scenarios (different method capabilities and transfer designs, 10,000 simulations per test). The results of the simulations showed that the method capability has a strong influence on the probability of success of its transfer. For the transfer design, the number of independent analytical runs to be performed on a same batch has much more influence than the number of replicates per run, especially when the inter-day variability of the method is high.

A classic descriptive approach for analytical method transfer does not take into account the variability of the method, and therefore, no risks are controlled.

Tools for designing analytical transfers and defining a new descriptive acceptance criterion, which take into account the intra- and inter-day variability of the method, are provided for a better risk evaluation by non-statisticians.
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Keywords: Analytical method transfer; Acceptance criteria; Method capability; HPLC assay; Monte Carlo simulations for risk analysis

1. Introduction

Analytical method transfer is defined as the complete process from the decision to transfer the method to another laboratory (called the Receiver) up to the official qualification of the Receiver by the laboratory that masters the method (called the Sender). This qualification will ensure that results obtained by the Receiver will be reliable.

Analytical transfer is now fully integrated into the life cycle of an analytical method in the pharmaceutical industry. However, even though the methodology is well described in ICH guidelines for a validation [1], no official guideline exists for a transfer methodology in pharmaceutical analysis.

According to the ICH Q9 guideline [1], risk analysis should be integrated into a transfer process. Setting acceptance criteria for an analytical transfer, however, is much more difficult than usually described. Some working groups in the pharmaceutical industry have offered different transfer methodologies (SFSTP [2] and ISPE [3]) for handling analytical transfer.

In general, analysis results on the same batch, obtained by the participating laboratories, are compared in terms of mean results and variability (in this paper, only the comparison of mean results is discussed). Statistical tools are available for data interpretation, however no tools are available for setting acceptance criteria and assessing their impact on the risks related to analytical transfer. Kringle et al. [4] described the different risks that have to be managed during the transfer, and compared the efficacy of different approaches for this risk control.

Criteria which are too wide may lead to the acceptance of a laboratory generating non-equivalent results (called the "poor"

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laboratory), resulting in bad release/reject decisions for pharmaceutical products (consumer risk = type I risk). Alternatively, criteria which are too tight may lead to the rejection of an equivalent laboratory (called the "good" laboratory), resulting in time costs and delay in the transfer process (industrial risk = type II risk). The most important risk to be taken into account is, obviously, the consumer risk. The industrial risk should not, however, be neglected.

With regards to the statistical tools, the most common approach (the "difference approach" with a Student's *t*-test) is still widely used within analytical laboratories, even though its inadequacy for analytical transfer has been proven (no control of the consumer risk) [2,4].

Equivalence tests are often offered as the alternative to the classical approach. This methodology permits a good control of the consumer risk, however it may also lead to an unacceptable industrial risk [4,5] that can only be partially controlled by multiplying the number of independent analytical runs to be performed in the transfer.

More sophisticated statistical approaches, with a full risk analysis, have also been described [6,7], but are not always easily applicable within laboratories lacking statisticians.

Where there are no statisticians available, the descriptive approach is generally used. This approach relies on a comparison of both the bias observed between the two laboratories and the variability observed in the receiving laboratory up to the limit values (acceptance criteria). With the classical descriptive approach, neither the type I nor type II risks are controlled [2,4,7].

This paper describes a new descriptive approach for analytical transfers and provides calculation tools to analysts in order to evaluate the main risks related to analytical transfers and to set one unique acceptance criteria according to those risks. This acceptance criterion, for the difference observed between two laboratories, which takes into account the method variability, is designed for each method to be validated. Different scenarios have therefore been defined, taking into account the results of the validation of the method to be transferred (capability of the method, repeatability and intermediate precision results). For each scenario, the results of the simulation of thousands of analytical transfers, performed using various assumptions, are provided. The utilisation of these results in order to undertake an analytical transfer with a non-statistical approach, but with a good evaluation of the risks, is described.

2. Theory

2.1. Variability of analytical methods

The variability of a method can be separated into:

(a) "intra-day" variations, characterised by $\hat{\sigma}_w^2$, the estimated within run variance, and by the repeatability Relative Standard Deviation (RSDr $= \hat{\sigma}_w/\hat{\mu}$, $\hat{\mu}$ being the estimated mean content value). These variations are usually calculated from one analytical run with several replicates for one batch, performed by one analyst on one equipment.

(b) "inter-day" variations, characterised by $\hat{\sigma}_B^2$, the estimated between run variance. These "inter-day" variations are usually calculated from independent analytical runs, performed by different analysts, on different equipment. Other sources of variation may be added.

The total variability of a method within a laboratory, estimated during the method validation, is characterised by the intermediate precision Relative Standard Deviation (RSDip $= (\hat{\sigma}_w + \hat{\sigma}_B)/\hat{\mu}$) that takes into account the intra- and inter-days variations.

The R.S.D. ratio of a method (ratio between RSDr and RSDip, determined during the validation) is an important characteristic for setting the best way to manage an analytical method transfer. Repeating analyses within the same run only offers additional information if this ratio is close to 1.0. If this is not the case, it is much more powerful to perform several independent analytical runs instead of performing several analyses within the same analytical run.

A survey performed on 77 validation reports of analytical methods (HPLC, GC, titrimetric, colorimetric and complexometric assays were involved) indicated that this ratio usually varied between 0.6 and 1.0. Some methods, however, showed a very high inter-day variability (with ratios varying from 0.1 to 0.5).

When this ratio for an analytical method is very low, it is clear that only a large number of independent determinations of content will give a good estimation of the true value for a given sample.

Additional variations, due to biases existing within each laboratory, may be estimated between laboratories. Usually, however, a method transfer is the first opportunity to have an estimation of the reproducibility of a method since the evaluation of this parameter is not required by ICH guidelines [1].

2.2. Capability of analytical methods

The variability of an analytical method can be compared to the product specifications in order to check its capability. This capability concept has been widely described in the literature, but its definition varies from one source to another [8,9].

In this article, the capability of an analytical method is defined and calculated as described in Eq. (1) [9]:

$$\mathrm{Cp} = \frac{\mathrm{TI}}{6\sigma} \tag{1}$$

TI is the tolerance interval of a measurement, and σ is the standard error of the measurement. When results are centred on 100%, which is the case for analytical methods for active ingredient or preservative content, Cp can be estimated from validation results and from the specifications of the compound to be analysed: TI is then the difference between the higher and lower specifications, and σ can be replaced by the intermediate precision R.S.D. (RSDip) (or, in order to avoid any underestimation of the variability of the method, by the upper value of the confidence interval calculated for RSDip).

Table 1
Identification of the 17 scenarios used for the simulations of analytical method transfers, with different method capabilities and different R.S.D. ratios, ratio between repeatability R.S.D. (RSDr) and intermediate precision R.S.D. (RSDip) of the method to be transferred (determined during the validation, see explanations in Section 2)

R.S.D. ratio (RSDr/RSDip)	Method capability value (Cp)				
	1.0	1.33	1.5	2.0	2.5
0.4	Scenario 1	Scenario 5	–	–	–
0.6	Scenario 2	Scenario 6	Scenario 9	Scenario 12	Scenario 15
0.8	Scenario 3	Scenario 7	Scenario 10	Scenario 13	Scenario 16
1.0	Scenario 4	Scenario 8	Scenario 11	Scenario 14	Scenario 17

It can be noted that with this definition, the capability of a method is the same (Cp = 2.0) when RSDip = 0.33% with specifications set at 98–102% (TI = 4%) or when RSDip = 0.83% with specifications set at 95–105% (TI = 10%) and when RSDip = 1.67% with specifications set at 90–110% (TI = 20%).

As defined, a 'six sigma' process achieves a Cp value of at least 2.0 [9]. The survey of the 77 method validation reports indicated that most of the Cp values are between 0.5 and 2.0 for methods used in pharmaceutical analysis. But for some methods, Cp could be as high as 9.3. These results showed a wide range of analytical variation, depending on the method and on the compound being analysed.

The simulations performed focussed on methods with Cp values within the most common range: from 1.0 to 2.5. Even though such methods are often used for pharmaceutical analysis, methods with Cp values inferior to 1.0 were not taken into account, due to their lack of capability. In these cases, a new method with a greater capability should be developed and validated in order to obtain more reliable results.

Methods with Cp values superior to 2.5 could be considered as having Cp = 2.5.

3. Experimental

3.1. Simulations of analytical transfers

3.1.1. Definition of 17 scenarios

Ten thousand analytical transfers were simulated for each of 17 different scenarios (see Tables 1 and 2), representative of the diversity of analytical methods to be transferred (different method capabilities and R.S.D. ratios, see Section 2.).

Table 2 describes, for the 17 defined scenarios, the R.S.D. values for an analytical method used for the determination of an active substance with specifications of 95–105% (corresponding to a tolerance interval TI = 10%). It can be noted that methods having RSDip over 1.67% are considered as lacking capability, and were not taken into account during the simulations.

Table 2
Repeatability R.S.D. values (for tolerance interval = 10%) corresponding to the 17 scenarios defined in Table 1

R.S.D. ratio	Method capability value (Cp)				
	1.0	1.33	1.5	2.0	2.5
0.4	0.67	0.50	–	–	–
0.6	1.00	0.75	0.67	0.50	0.40
0.8	1.33	1.00	0.89	0.67	0.53
1.0 (RSDr = RSDip)	1.67	1.25	1.11	0.83	0.67

R.S.D. ratio is the ratio between repeatability R.S.D. (RSDr) and intermediate precision R.S.D. (RSDip) of the method to be transferred.

3.1.2. Design of the simulations

Simulations were designed to represent a classic analytical method transfer design: the same batch of the product to be analysed was provided to both the Sender and Receiver laboratories. Within each laboratory, independent analytical runs were performed (in order to evaluate inter-run variability due to changes of mobile phase, calibration, equipment, analyst, day, etc.) with several replicates per analytical run (different weighing and preparation of the product to be analysed). For each scenario, n independent analytical runs with p replicates per run were simulated in the 2 different laboratories (Receiver and Sender), with n and p varying as follows:

$$n = 2, 3, 4, 5, 6 \text{ and } 7$$

$$p = 3, 4, 5 \text{ and } 6.$$

For each simulated analytical run, within run and between run variability were taken into account.

For each replicate of each analytical run, and for each laboratory, the simulated content value was taken at random from the variable $N((100 - \bar{X}_i),\ \text{RSDr})$, $\bar{X}_i$ being simulated, for each analytical run from a variable $N(0, \hat{\sigma}_B)$ in order to take into account the inter-run variability of the method.

After each simulation, the variable corresponding to observed bias Bias_{obs} (difference between the mean of $n \times p$ content values at the Sender and Receiver laboratories) was studied.

Observed bias was due only to the differences in evaluation of the actual content in the sample studied.

These simulations assumed that the real bias Bias_{real} between the 2 laboratories was null. Evaluation of the impact of a real bias was then performed by calculation only.

3.2. Distribution fitting from simulated data

For each simulation, the 10,000 values observed for the variable Bias_{obs} fitted to a Normal distribution. For each set of simulation, the standard error of the simulated variable was determined (and named σ_{obs}).

Table 3
Calculated standard error (σ_{obs}) of the simulated variable "observed bias" ($Bias_{obs}$) for a method with capability Cp = 1.0 (tolerance interval = 10%)

R.S.D. ratio	Number of replicates per run (p)	Number of independent analytical runs (n)					
		2	3	4	5	6	7
0.4	3	1.57	1.29	1.12	1.00	0.91	0.84
	4	1.55	1.27	1.11	0.99	0.90	0.83
	5	1.54	1.27	1.10	0.98	0.89	0.83
	6	1.54	1.26	1.10	0.98	0.89	0.82
0.6	3	1.46	1.18	1.03	0.92	0.84	0.78
	4	1.43	1.16	1.01	0.91	0.83	0.77
	5	1.42	1.15	1.00	0.90	0.82	0.76
	6	1.41	1.14	1.00	0.89	0.82	0.75
0.8	3	1.28	1.05	0.90	0.80	0.73	0.68
	4	1.22	0.99	0.86	0.76	0.70	0.64
	5	1.18	0.96	0.83	0.74	0.67	0.62
	6	1.16	0.94	0.81	0.72	0.66	0.61
1.0	3	0.97	0.80	0.69	0.62	0.56	0.52
	4	0.85	0.69	0.60	0.53	0.48	0.45
	5	0.76	0.62	0.54	0.48	0.44	0.40
	6	0.69	0.56	0.49	0.44	0.40	0.37

R.S.D. ratio is the ratio between repeatability R.S.D. (RSDr) and intermediate precision R.S.D. (RSDip) of the method to be transferred.

3.3. Software

The simulations, using the Monte Carlo algorithms, and the distribution fitting were performed with Crystal Ball software (version 2000.51, edited by Decisioneering, www.crystalball.com).

Calculations were performed by Microsoft® Excel 2000, with the NORMDIST function.

All the calculations were performed with the following assumption: TI = 10.0% (corresponding to 95.0–105.0% specifications).

4. Results of the simulations

Different simulation scenarios were performed, according to values given in Table 2 (with TI = 10%).

For each of the 10,000 simulations, the value of $Bias_{obs}$ was calculated. The observed values fitted to a Normal distribution, centred as assumed on 0, with a calculated variance σ^2_{obs} depending on the capability of the method (Cp) and on the number of determinations (n and p). These values of σ_{obs}, determined by distribution fitting for each set of simulations (for each scenario and each of the n and p values) are given in

Table 4
Calculated standard error (σ_{obs}) of the simulated variable "observed bias" ($Bias_{obs}$) for a method with capability Cp = 1.33 (tolerance interval = 10%)

R.S.D. ratio	Number of replicates per run (p)	Number of independent analytical runs (n)					
		2	3	4	5	6	7
0.4	3	1.18	0.96	0.83	0.75	0.69	0.64
	4	1.17	0.95	0.83	0.74	0.68	0.63
	5	1.17	0.95	0.82	0.74	0.68	0.63
	6	1.16	0.94	0.82	0.73	0.68	0.63
0.6	3	1.07	0.89	0.77	0.69	0.63	0.58
	4	1.05	0.87	0.75	0.67	0.61	0.57
	5	1.04	0.86	0.74	0.67	0.61	0.56
	6	1.03	0.85	0.74	0.66	0.60	0.56
0.8	3	0.94	0.77	0.66	0.60	0.54	0.50
	4	0.89	0.73	0.63	0.57	0.51	0.47
	5	0.86	0.70	0.61	0.55	0.50	0.46
	6	0.84	0.69	0.60	0.54	0.49	0.45
1.0	3	0.72	0.59	0.51	0.46	0.41	0.38
	4	0.63	0.51	0.44	0.40	0.36	0.33
	5	0.56	0.46	0.40	0.36	0.32	0.30
	6	0.52	0.42	0.37	0.33	0.30	0.27

R.S.D. ratio is the ratio between repeatability R.S.D. (RSDr) and intermediate precision R.S.D. (RSDip) of the method to be transferred.

Table 5
Calculated standard error (σ_{obs}) of the simulated variable "observed bias" ($Bias_{obs}$) for a method with capability Cp = 1.5 (tolerance interval = 10%)

R.S.D. ratio	Number of replicates per run (p)	Number of independent analytical runs (n)					
		2	3	4	5	6	7
0.6	3	0.97	0.79	0.69	0.62	0.57	0.53
	4	0.95	0.77	0.68	0.61	0.55	0.51
	5	0.94	0.77	0.67	0.60	0.54	0.51
	6	0.93	0.76	0.66	0.59	0.54	0.50
0.8	3	0.84	0.69	0.59	0.53	0.48	0.45
	4	0.80	0.65	0.56	0.50	0.46	0.43
	5	0.77	0.63	0.54	0.48	0.44	0.41
	6	0.75	0.62	0.53	0.47	0.43	0.40
1.0	3	0.65	0.53	0.46	0.41	0.37	0.35
	4	0.57	0.46	0.40	0.36	0.32	0.30
	5	0.50	0.41	0.35	0.32	0.29	0.27
	6	0.46	0.37	0.32	0.29	0.26	0.24

R.S.D. ratio is the ratio between repeatability R.S.D. (RSDr) and intermediate precision R.S.D. (RSDip) of the method to be transferred.

Table 6
Calculated standard error (σ_{obs}) of the simulated variable "observed bias" ($Bias_{obs}$) for a method with capability Cp = 2.0 (tolerance interval = 10%)

R.S.D. ratio	Number of replicates per run (p)	Number of independent analytical runs (n)					
		2	3	4	5	6	7
0.6	3	0.72	0.58	0.51	0.45	0.42	0.39
	4	0.70	0.57	0.50	0.44	0.41	0.38
	5	0.69	0.56	0.49	0.44	0.40	0.38
	6	0.69	0.56	0.49	0.43	0.40	0.37
0.8	3	0.62	0.51	0.44	0.39	0.36	0.33
	4	0.59	0.48	0.42	0.37	0.34	0.32
	5	0.57	0.47	0.40	0.36	0.33	0.31
	6	0.56	0.46	0.40	0.35	0.32	0.30
1.0	3	0.48	0.39	0.34	0.30	0.28	0.25
	4	0.42	0.34	0.29	0.26	0.24	0.22
	5	0.37	0.30	0.26	0.24	0.22	0.20
	6	0.34	0.27	0.24	0.21	0.20	0.18

R.S.D. ratio is the ratio between repeatability R.S.D. (RSDr) and intermediate precision R.S.D. (RSDip) of the method to be transferred.

Table 7
Calculated standard error (σ_{obs}) of the simulated variable "observed bias" ($Bias_{obs}$) for a method with capability Cp = 2.5 (tolerance interval = 10%)

R.S.D. ratio	Number of replicates per run (p)	Number of independent analytical runs (n)					
		2	3	4	5	6	7
0.6	3	0.59	0.48	0.41	0.37	0.34	0.31
	4	0.58	0.47	0.41	0.36	0.33	0.31
	5	0.57	0.47	0.40	0.36	0.33	0.31
	6	0.57	0.46	0.40	0.36	0.33	0.30
0.8	3	0.51	0.42	0.36	0.32	0.30	0.27
	4	0.49	0.40	0.34	0.31	0.28	0.26
	5	0.47	0.39	0.33	0.30	0.27	0.25
	6	0.46	0.38	0.33	0.29	0.27	0.24
1.0	3	0.39	0.32	0.28	0.25	0.22	0.21
	4	0.34	0.28	0.24	0.21	0.19	0.18
	5	0.30	0.25	0.21	0.19	0.17	0.16
	6	0.28	0.23	0.20	0.17	0.16	0.15

R.S.D. ratio is the ratio between repeatability R.S.D. (RSDr) and intermediate precision R.S.D. (RSDip) of the method to be transferred.

Tables 3–7 (one table per method capability value, as defined in Table 1).

In can be observed, in Tables 3–7, that values of σ_{obs} were strongly dependant on the Cp value and on the RSDr/RSDip ratio. The influence of the number of independent analytical runs, n, is also very important. An increase of the number of replicates, p, may have a slight effect, but only for high RSDr/RSDip ratios (ratio ≥ 0.8).

5. Discussion

As explained in Section 2, the calculations and interpretation of the simulation data can be extrapolated to methods with different TI. For example, for a method used for preservatives (specifications set at 90.0–110.0%), the tolerance interval is doubled (TI = 20.0%). The σ_{obs} values in Tables 3–7 are doubled, and the acceptance criteria can then also be doubled. The corresponding probabilities of success will thus be unchanged.

5.1. Simulated data interpretation

5.1.1. Graphical example for Scenario 14

For Scenario 14 (see Table 1) the analytical method had a Cp value of 2.0. This method could then be considered as a "Six Sigma process", ensuring very reliable results. One could feel confident about the results of an analytical transfer in this case.

Fig. 1 illustrates, for Scenario 14, the results of the 10,000 simulations and, from these results, the probability of success of an analytical transfer with a Receiver laboratory having a null actual bias, with an acceptance criteria (AC) set at 1.0%. The dark zone (probability of accepting the laboratory, which is a "good" one since the actual bias is null) represented 96.4% of the 10,000 analytical transfers.

In this case, the probability of refusing a "good" laboratory (grey zone in Fig. 1) is limited to 3.6%.

Fig. 2 illustrates, for an actual bias ($Bias_{real}$) set at 0.5%, the same probabilities: the grey zone represents 14.9% of the 10,000 simulations. The probability of rejecting the laboratory is nearly 15%, with an actual bias of 0.5%, which would nevertheless be considered as analytically acceptable.

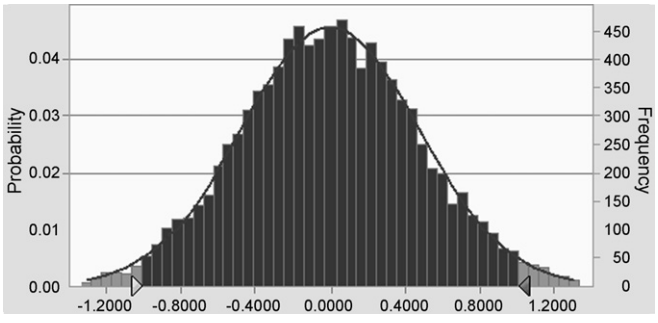

Fig. 1. Bias observed between sender and receiver laboratories for 10,000 simulations of analytical method transfers with Scenario 14 (see Table 1), with 2 independent analytical runs and 3 replicates per run). The dark area represents the probability of accepting the receiving laboratory (96.4%) when acceptance criteria is set at 1.0% and when the actual bias between both laboratories is null.

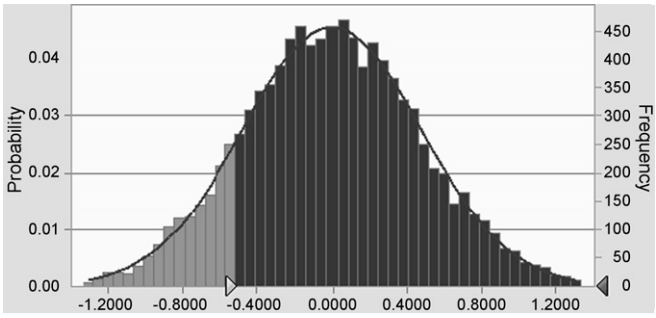

Fig. 2. Bias observed between sender and receiver laboratories for 10,000 simulations of analytical method transfers with Scenario 14 (see Table 1), with 2 independent analytical runs and 3 replicates per run). The dark area represents the probability of accepting the receiving laboratory (85.1%) when acceptance criteria is set at 1.0% and when the actual bias between both laboratories is set at 0.5%.

It can easily be seen, from Figs. 1 and 2, that for a real bias of 1.0% between the two laboratories, 50% of the transfers will be considered as acceptable while the other 50% would generate a refusal of the receiving laboratory.

5.1.2. General interpretation

The Normal distribution fitting to $Bias_{obs}$ data obtained by simulation has a standard error, σ_{obs}. From these σ_{obs} values (see Tables 3–7) are calculated, depending on the acceptance criteria and on the real bias, the probability of accepting a poor laboratory (type I error) and, on the other hand, the probability of refusing a good laboratory (type II error).

The probability of success of an analytical transfer (probability of accepting the receiving laboratory), for an acceptance criteria, AC and an actual bias, $Bias_{real}$ is the area of the Normal distribution $N(0, \sigma_{obs})$ between the values $(-AC + Bias_{real})$ and $(+AC + Bias_{real})$.

This probability P can be calculated with the NORMDIST function in Excel, as described in Eq. (2)

$$P = \text{NORMDIST}(AC + Bias_{real}, \sigma_{obs}, 0, \text{true}) - \text{NORMDIST}(-AC + Bias_{real}, \sigma_{obs}, 0, \text{true}) \quad (2)$$

In Eq. (2), σ_{obs} is dependant on the method capability and the transfer design (Cp, n and p, as shown in Tables 3–7), and the final calculation depends on the acceptance criteria and the actual bias $Bias_{real}$ between the laboratories. When $Bias_{real}$ is above the acceptance criteria, the probability calculated can be considered as the risk of accepting a "poor" laboratory (type I risk), and when $Bias_{real}$ is below the acceptance criteria, the probability calculated is the probability of accepting a "good" laboratory (from which can be calculated the risk of refusing this good laboratory, type II risk).

5.2. Probability of success and risk analysis

5.2.1. Critical review of the classic descriptive approach

With the classic descriptive approach, the acceptance criteria is set regardless of the variability of the method to be transferred. Table 8 represents the probability of success of an analytical

Table 8
Probability (%) of concluding that bias observed during the transfer is acceptable (with acceptance criteria set at 2.0%), depending on the calculated standard error σ_{obs} (fitted from the simulated variable "observed bias", $Bias_{obs}$) and for different real bias ($Bias_{real}$) between sender and receiver laboratories

$Bias_{real}$	Standard error of the variable $Bias_{obs}$, σ_{obs}					
	0.20	0.40	0.70	1.00	1.20	1.40
0	>99	>99	>99	95	90	85
0.5	>99	>99	98	93	88	82
1.0	>99	99	92	84	79	75
1.5	99	89	76	69	66	63
2.0	50	50	50	50	50	50
2.2	16	31	39	42	43	44
2.5	1	11	24	31	34	36
3.0	<1	1	8	16	20	24
3.5	<1	<1	2	7	11	14

method transfer for different σ_{obs} values, representative of those presented in Tables 3–7, when the acceptance criteria is set at 2.0 (as recommended in ref. [3]).

When the real bias $Bias_{real}$ between the Sender and Receiver laboratories is equal to the acceptance criteria, the probability of success is 50%, as expected. When $Bias_{real}$ is very slightly over the acceptance criteria (2.2), it should be noted that the type I risk (consumer risk), which is already above 15% with $\sigma_{obs} = 0.20$, increases dramatically with the σ_{obs} values. When σ_{obs} is at or above 1.0, the risk of accepting a laboratory with an unacceptable Real bias of 3.5% is not negligible. On the other hand, the type II risk also increases with σ_{obs} values, and this industrial risk should not be neglected either.

These results, which confirm those presented in the literature [4,5], illustrate the absence of risk control with the classic descriptive approach, and show that the transfer study design (number of independent analytical runs and number of replicates per run) should be adapted to the variability of the method to be transferred (characterised here by its capability Cp and the RSDr/RSDip ratio).

Analysis of the influence of the number of independent analytical runs (n) and of the method capability on the probability of success of the transfer was therefore analysed for the simulated data.

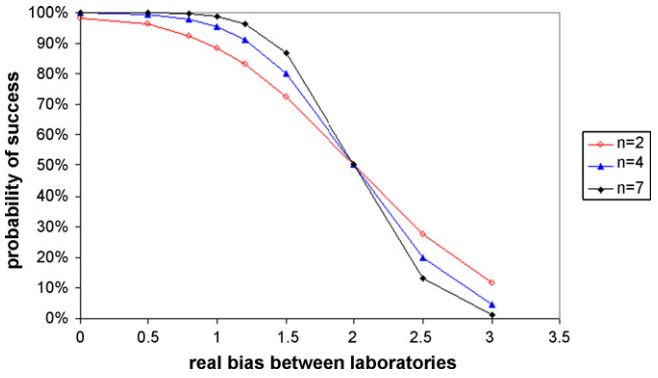

Fig. 3. Influence of the number of analytical runs ($n = 2$, 4 or 7, with 3 replicates per run) on the probability of success of an analytical transfer (for Scenario 10, see Table 1). Acceptance criteria is set at 2.0%.

5.2.2. *Influence of increasing the number of analytical runs (n) on the probability of success of an analytical transfer*

Fig. 3 illustrates, for Scenario no. 10 (one of the most common scenarios, according to a survey of 77 validation reports) with TI = 10.0% and $p = 3$, the influence of increasing n on the probability of success for a transfer, when the acceptance criteria is set at 2.0 (using Eq. (2)).

It can be noted, in the example in Fig. 3 (and in Table 9), that increasing n from 2 to 4 ensures a much better decision for the analytical transfer. Increasing n above 4 will decrease both type I and type II risks, although this evolution is less when $n > 4$.

This result has a direct influence on the study design.

Setting $n = 4$ can be managed, within each laboratory, as follows: 2 different analysts perform p replicates at 2 different times. Furthermore, crossing equipment between the two analysts between run 1 and run 2 will allow a better estimation of the whole laboratory variability, and therefore lead to a good transfer decision.

5.2.3. *Influence of the method capability on the probability of success of an analytical transfer*

In Fig. 4, the influence of the Cp value on the probability of success of an analytical transfer is represented (for $n = 4$, $p = 3$, TI = 10%, RSDr/RSDip = 0.8 and AC = 2.0%). This parameter, which has to be evaluated before setting the acceptance criteria, has a very strong influence on the transfer results.

Table 9
Probability of success for an analytical method transfer for Scenario 10 (see Table 1), depending on the acceptance criteria and the real bias between the sender and receiver laboratories ($Bias_{real}$), with the number of independent run (n) varying from 2 to 5, and 3 replicates per run

$Bias_{real}$	AC = 1.0%				AC = 2.0%				AC = 3.0%			
	$n=2$	$n=3$	$n=4$	$n=5$	$n=2$	$n=3$	$n=4$	$n=5$	$n=2$	$n=3$	$n=4$	$n=5$
0	77	85	91	94	98	>99	>99	>99	>99	>99	>99	>99
0.5	69	75	80	83	96	99	>99	>99	>99	>99	>99	>99
1.0	49	49	50	50	88	93	95	97	99	>99	>99	>99
1.5	27	23	20	17	72	77	80	83	96	99	99	>99
2.0	12	7	5	3	50	50	50	50	88	93	95	97
2.2	8	4	2	1	41	39	37	35	83	88	91	94
2.5	4	1	1	<1	28	23	20	17	72	77	80	83
3.0	1	<1	<1	<1	12	7	5	3	50	50	50	50
3.5	<1	<1	<1	<1	4	1	1	<1	28	23	20	17

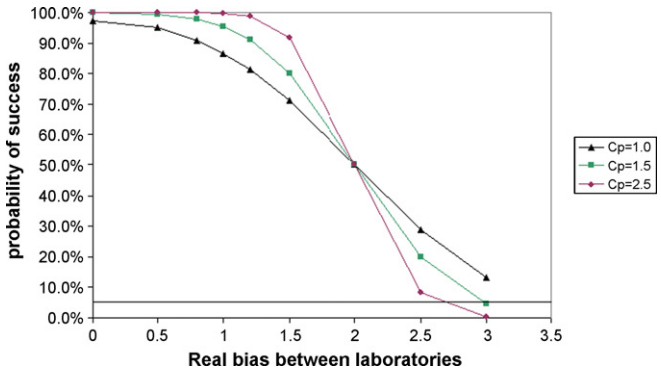

Fig. 4. Influence of capability of the method on the probability of success of an analytical transfer (with 4 analytical runs of 3 replicates per laboratory). Repeatability to intermediate precision R.S.D. ratio is set at 0.8. Acceptance criteria is set at 2.0%.

The higher the value of Cp, the higher the probability of the transfer's success.

Methods with a low Cp value will induce high type I and type II risk levels, and the analytical transfer should, in that case, be replaced by a new method validation, after redevelopment of a method having a better capacity, as described by Dejaegher et al. [10].

5.2.4. *Influence of acceptance criteria on the probability of success of an analytical transfer*

In Table 9, the calculation results for Scenario 10 (same assumptions as for Section 5.2.2 and Fig. 3) are presented in another manner, which can give a decision tool to those setting up an analytical method transfer. These results are comparable with those described by Kringle et al. [4], with a scenario similar to Scenario 10.

Setting a tight acceptance criteria (AC = 1.0%) will ensure a rejection of any poor laboratory (probability of accepting a laboratory with an actual bias $\text{Bias}_{\text{real}} \geq 3.0\%$ is at or below 1%). But the probability of accepting a good laboratory with $\text{Bias}_{\text{real}} = 0.5\%$ drops down to 69% (for $n = 2$).

Setting a wide acceptance criteria (AC = 3.0%) will ensure an acceptance of all the laboratories with $\text{Bias}_{\text{real}} \leq 1.0\%$, but with a 50% risk of accepting laboratories with $\text{Bias}_{\text{real}} = 3.0\%$, which is unacceptable with respect to the consumer risk.

Setting the acceptance criteria AC = 2.0% (for the quoted example) with $n = 4$ ensures a low probability for both type I and type II risks.

5.3. *Setting acceptance criteria with a new descriptive approach*

For a method with TI = 10.0%, an acceptance criteria of 3.0% is commonly used in the pharmaceutical industry, as described in the literature [2].

Having a real bias at or over 3.0% may indeed lead to a number of false negative results (out of specification results, producer risk) or, even worse, to false positive results (release of out of specification batches, consumer risk).

When used within a laboratory, this 3.0% acceptance criteria is generally understood as follows: any laboratory with a real bias over 3.0% will be rejected, and laboratories with a real bias below 3.0% will be accepted. But, as shown in Tables 8 and 9, it is unfortunately impossible to estimate the real bias from the bias observed during an analytical transfer. The mean values obtained within each laboratory are only an estimation of the true value. The variability of the difference is therefore higher than the variability within each laboratory.

The only result that can be predicted is the probability of accepting a laboratory where the actual bias $\text{Bias}_{\text{real}} = \text{AC}$, the acceptance criteria, which is equal to 50%, as shown in Fig. 3.

This result shows that the acceptance criteria must be set below the maximum acceptable real bias.

Since the aim of a transfer is to limit the risk of accepting a poor laboratory (taken here as a laboratory with a real bias at or above 3.0%), with a limitation of consumer risk (type I risk) below 5%, it is important, for each analytical transfer, to analyse the results of the validation of the method to be transferred.

The analysis of the validation results allows the determination of the Cp and of the RSDr/RSDip ratio, in order to choose the scenario (Tables 1 and 2) corresponding to the method to be transferred.

Analysis of the Normal distribution $N(0, \sigma_{\text{obs}})$, as shown in Fig. 3, and/or the calculation of the probabilities of success according to Eq. (2), will thus allow the definition of an acceptance criteria AC (below the maximum acceptable real bias of 3.0%) in order to limit the type I risk at or below 5.0%.

This exercise was performed for each of the 17 scenarios: σ_{obs} results obtained during the simulations (Tables 3–7) were computed using Eq. (2) with $n = 4$, AC varying from 1.1 to 2.7 and with $\text{Bias}_{\text{real}}$ set at 3.0%. The highest AC values allow-

Table 10
Acceptance criteria values to be set for an analytical transfer ($n = 4$, TI = 10.0%) for the 17 scenarios (see Table 1), for having type I risk at or below 5.0% for $\text{Bias}_{\text{real}} = 3.0\%$

R.S.D. ratio	Number of replicates per run (p)	Method capability value (Cp)				
		1.0	1.33	1.5	2.0	2.5
0.4	3	1.1	1.6	–	–	–
	4	1.1	1.6	–	–	–
	5	1.1	1.6	–	–	–
	6	1.1	1.6	–	–	–
0.6	3	1.2	1.7	1.8	2.1	2.3
	4	1.3	1.7	1.8	2.1	2.3
	5	1.3	1.7	1.8	2.1	2.3
	6	1.3	1.7	1.9	2.1	2.3
0.8	3	1.5	1.9	2.0	2.2	2.4
	4	1.5	1.9	2.0	2.3	2.4
	5	1.6	1.9	2.1	2.3	2.4
	6	1.6	2.0	2.1	2.3	2.4
1.0	3	1.8	2.1	2.2	2.4	2.5
	4	2.0	2.2	2.3	2.5	2.6
	5	2.1	2.3	2.4	2.5	2.6
	6	2.2	2.3	2.4	2.6	2.6

R.S.D. ratio is the ratio between repeatability R.S.D. (RSDr) and intermediate precision R.S.D. (RSDip) of the method to be transferred.

Table 11
Probability of success for an analytical transfer with a laboratory having an acceptable real bias of 0.5% ($n = 4$, TI = 10.0%) for the 17 scenarios (see Table 1). A probability below 90% corresponds to a type II risk above 10%

R.S.D. ratio	Number of replicates per run (p)	Cp value				
		1.0	1.33	1.5	2.0	2.5
0.4	3	63	90	–	–	–
	4	63	90	–	–	–
	5	63	90	–	–	–
	6	64	91	–	–	–
0.6	3	70	94	97	>99	>99
	4	75	94	97	>99	>99
	5	75	95	97	>99	>99
	6	75	95	98	>99	>99
0.8	3	85	98	99	>99	>99
	4	87	99	>99	>99	>99
	5	90	99	>99	>99	>99
	6	91	99	>99	>99	>99
1.0	3	97	>99	>99	>99	>99
	4	99	>99	>99	>99	>99
	5	>99	>99	>99	>99	>99
	6	>99	>99	>99	>99	>99

R.S.D. ratio is the ratio between repeatability R.S.D. (RSDr) and intermediate precision R.S.D. (RSDip) of the method to be transferred.

ing a probability of success at or below 5% are presented in Table 10.

It is noticeable that an increase of the number of replicates per analytical run has a very low influence on the result, compared to the influence of the capability of the method and of the RSDr/RSDip ratio, calculated from the validation results.

It is clear that setting a low AC value will not only limit type I risk, but also increase type II risk. Therefore, at the AC level used, the probability of success for a laboratory having an acceptable real bias $Bias_{real} = 0.5\%$ was calculated in order to evaluate this type II risk (producer risk). The results are presented in Table 11.

All the calculations presented here are assuming that the evaluation of the method variability during the method validation (calculation of RSDr and of RSDip) is reliable. The extent of reliability may depend on the validation design, but is out of the scope of this paper. Any additional data obtained during the use of the method may confirm or consolidate the data obtained during the validation.

6. Conclusion

The usual descriptive approach for an analytical transfer does not allow a powerful analysis of the different risks related to the analytical transfer, *i.e.* type I risk (risk of accepting a "poor" laboratory, which may lead to a consumer risk) and type II risk (risk of refusing a good laboratory, which consumes time and money for the producer).

Making simulations (or calculations from the results of the simulations performed and described in Tables 3–7) before setting descriptive acceptance criteria can lead to a precise estimation of these risks, and therefore, is acceptable for authorities and for analytical laboratories.

A design with 4 analytical runs with 3 replicates per run may be suitable for most of the methods to be transferred. The mean results of each laboratory will be compared to the acceptance criteria defined for the bias observed between the laboratories (criteria that takes into account the method variability).

Furthermore, when designing the analytical transfer, sources of variations such as analysts and equipment can be tested. The Sender laboratory can then have a good estimation of the global variability of the method in the Receiver laboratory. This variability can be expressed as RSDr and RSDip in the Receiver laboratory, just as during a method validation, and the results can also be compared to descriptive acceptance criteria, as defined by the different working groups of the pharmaceutical industry [2,3,11].

With this new descriptive approach, it is possible for the transfer team in charge of the analytical transfer to choose the scenario that fits the validation results of the method to be transferred, and to calculate from the results of the simulations the acceptance criteria that best suits the purpose of the transfer.

This unique acceptance criterion already takes into account the variability of the analytical method to be transferred, and is therefore an easy decision tool for the transfer team.

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