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The transfer of a LC-UV method for the determination of fenofibrate and fenofibric acid in Lidoses: Use of total error as decision criterion

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Abstract

Two new statistical approaches to assess the validity of the transfer of a LC-UV method for the determination of fenofibrate and fenofibric acid were investigated and compared to the conventional approaches generally used in this domain. These new approaches, namely the Tolerance Interval and the Risk approaches, are based on the simultaneous evaluation of the systematic (or trueness) and random (or precision) errors of the transfer into a single criterion called total error (or accuracy). The results of the transfer showed that only the total error based approaches fulfilled the objective of an analytical method transfer, i.e. to give guarantees that each future measurement made by the receiving laboratory will be close enough to the true value of the analyte in the sample. Furthermore the Risk approach was the most powerful one and allowed the estimation of the risk to have future measurements out of specification in the receiving laboratory, therefore being a risk management tool.

Keywords: Analytical method transfer; Transfer methodology; Tolerance interval; Risk; Statistical approaches

1. Introduction

The transfer of a method from a laboratory to a production site is an important step in the development cycle of new pharmaceutical products. It is increasingly used due to the economical pressure coming from the rationalization of production sites, analytical subcontracting and fusion of pharmaceutical groups.

Transferring an analytical method of control requires not only transferring the procedure physically from a laboratory that masters the technique (called sender) to another site (called receiver) but also the qualification of this receiving laboratory. The receiver must give guarantees that he has the capacity to implement the method and much more that he is able to obtain reliable results.

The pharmaceutical industry is highly controlled, and the competent authorities are pushing for a better regulation and formalization of these transfers [1]. In order to achieve this, some groups have published recommendations and guidelines [2,3] on how to conduct an analytical transfer. In these protocols, the qualification of the receiving laboratory is performed through various statistical approaches [3].

These statistical approaches rely on the dissociated analysis of the trueness and the precision criterion of the transfer. Three conventional approaches are used: the descriptive, the difference and the equivalence approaches. The disadvantages of these statistical approaches are that they do not control or partially control the type I and/or type II errors (producer and consumer risks) [4], they behave illogically [4], some of them may detect differences that are not analytically significant [3] and they do not allow the compensation of a systematic error by a smaller random error (and vice versa) [5].

Furthermore, as the objective of an analytical transfer is to give guarantees that each future measurement made by the

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receiving laboratory will be close enough to the true value of the analyte in the samples, these classical approaches do not fulfill this objective [5,6].

Therefore, two recently developed statistical approaches that alleviate those problems by relying on the total error (or accuracy) as decision criterion were applied [5,6]. The two approaches are the Tolerance Interval approach and the Risk approach. They combine simultaneously random errors (or precision) and systematic errors (or trueness) in a single term.

These novel approaches were integrated in a transfer protocol based on published recommendations and compatible with the practices and requirements of the industry. This protocol was applied and then evaluated on the transfer of a LC-UV method for the determination of fenofibrate and fenofibric acid in Lidoses. Finally, these statistical approaches were compared to the other conventional techniques: the descriptive approach, the difference approach and the equivalence approach.

2. Experimental

2.1. Chemicals and solvents

All chemicals and solvents used were of analytical or HPLC grade. Fenofibrate and fenofibric acid were supplied by the European Pharmacopoeia (Strasbourg, France). Potassium dihydrogen phosphate was purchased from Acros Organics (Geel, Belgium). Methanol and phosphoric acid (85%) were obtained from Merck (Darmstadt, Germany). Deionized water was generated from Milli-Q water purifying system (Millipore, Watford, UK). Phosphate buffer pH 4.5 was prepared by dissolving 6.8 g of potassium dihydrogen phosphate in 1.0 l of deionized water. The pH was adjusted to 4.5 with phosphoric acid.

2.2. Apparatus

At the sending site, the analyses were performed on an Agilent technologies HPLC 1100 series (Hewlett-Packard, Palo-Alto, CA, USA) equipped with a solvent delivery quaternary pump G1311A, an on-line degasser G1322A, an autosampler G1313A, a column oven G1316A and a diode-array detector G1315A. A computer Hewlett-Packard Kayak XA using the software for HPLC Chemstation® was used to control the whole chromatographic system and to acquire, process and store all the data obtained.

At the receiving site, two different liquid chromatography systems were used to perform the analysis. One was similar to the one used at the sending laboratory and the other one was an Agilent technologies HPLC 1100 series consisting of a solvent delivery binary pump G1312A, an autosampler G1313A, a column oven G1316A and a diode array detector G1315A. This HPLC system was interfaced with a computer Hewlett-Packard Vectra XM using the software for HPLC Chemstation® to control the entire chromatographic system and to acquire, process and store all the data obtained.

2.3. Chromatographic conditions

The chromatographic analysis was performed on a Lichrospher 100 RP-8 column (125 mm × 4 mm i.d., 5 μm particle size) and kept at 35 °C. The mobile phase was prepared by mixing methanol and phosphate buffer (pH 4.5) in a ratio 70:30 (v/v) and was degassed before use. The HPLC system was operated isocratically at a flow rate of 0.8 ml/min and the injection volume was 50 μl. UV detection was performed at 288 nm and peaks were identified with retention times and UV spectra.

2.4. Standard solutions

A stock solution of fenofibrate was prepared by accurately weighting 20.0 mg of fenofibrate and diluting this in 25.0 ml of methanol. The calibration standards for fenofibrate were prepared by diluting the stock solution with a phosphate buffer pH 4.5/methanol mixture (50:50, v/v) to reach the concentration level of 80.0 μg/ml. The validation standards were prepared in reconstituted solutions to reach five concentration levels: 40, 60, 80, 100 and 120 μg/ml.

Approximately 4.0 mg of fenofibric acid was accurately weighted and diluted to 50.0 ml with methanol. The calibration standards were prepared by diluting an aliquot of this stock solution with a mixture of phosphate buffer pH 4.5 and methanol (50:50, v/v) to reach the concentration of 400 ng/ml. The validation standards were prepared in reconstituted solutions also at five concentration levels: 80, 200, 400, 800 and 1600 ng/ml.

2.5. Sample preparation

The content of ten Lidoses was extracted and gently softened. A portion of the pasty mass equivalent to about 40 mg of fenofibrate was accurately weighted, dissolved and diluted to 50.0 ml with methanol. The sample solution was prepared by mixing 2.0 ml of this solution with a phosphate buffer pH 4.5/methanol mixture (50:50, v/v) up to a final volume of 20.0 ml. The theoretical concentration of fenofibrate is 80.0 μg/ml.

2.6. Computations

The validation data were processed with the software e-noval® version 1.1a (Arlenda s.a., Liège, Belgium). The transfer simulations and computations were performed with the software SAS® version 8.2 (SAS Institute, Tervuren, Belgium).

2.7. Transfer design

According to the transfer protocol, a familiarization step has been implemented before the realization of any dosage by the receiving laboratory. This step involved the training of the analysts by and on the sending site, completed with the execution of the analytical method by the receiving laboratory.

Then the formal transfer experiments were launched. The transferred analytical method was previously fully validated by

the sending laboratory. The performances of the method, in terms of accuracy, trueness and precision, are therefore known and have been accepted according to the objective of the method. What is consequently required, at the receiving site, is to make sure that the results are coherent with the performances of the sending site. With this intention, one batch of the speciality of interest was used for the transfer. This batch has previously been analyzed by the sender and the set of data generated was used as a basis for the comparison of the results obtained by the receiving laboratory according to the two total error approaches. An evaluation of the receiving site's performances could then be carried out. The pre-specified acceptance limits were set for the total error approaches at 5 and 10% for fenofibrate and fenofibric acid, respectively since we are working with a drug product and with an impurity. The minimum expected proportion of results to fall inside these acceptance limits was set at 0.90 (β) and the maximum risk tolerated at 0.10 ($1-\beta$) for both analytes. For the conventional statistical approaches, the acceptance limits were set at 2 and 3% concerning fenofibrate and at 10 and 30% for fenofibric acid for the precision and trueness criteria, respectively, in accordance with the limits proposed in the SFSTP guide [3].

In order to reproduce as well as possible the sources of inter-series variation which are likely to be met during the routine use of the analytical procedure at the receiving site, two operators using two different HPLC equipments, carried out the series of experiments.

Furthermore, to select the most appropriate numbers of series and runs to perform in each laboratory with the total error approaches, the experimental design was worked out on the basis of bootstrap simulations. Using the values of the relative standard deviation of repeatability ($R.S.D._{REP}$) and intermediate precision ($R.S.D._{IP}$) estimated during the validation step of the method, Normally distributed random data were generated with the SAS function rannor. Those data have been generated for different levels of supposed true bias between the two laboratories involved ranging from 0 to 3%. In order to increase the robustness of the relative standard deviation (R.S.D.) chosen for the realization of the simulated transfers, the averages of the R.S.D. obtained during the validation of the method were taken. The statistical analysis of the data was then carried out according to the new approaches based on the total error, by specifying acceptance limits of 5% for fenofibrate and 10% for fenofibric acid. Finally, the proportion of accepted transfers has been calculated. This exercise was repeated for various combinations of numbers of series and repetitions in order to determine the adequate one. Table 1 shows the different conditions assessed during the simulations.

Table 1
Conditions used for the simulations of the transfer

# Series for the receiver	3; 5; 7; 9
# Series for the sender	1
# Repetitions per series	3
($R.S.D._{REP}$%; $R.S.D._{IP}$%)	(0.5; 0.5); (1; 1)
Bias (%)	0, 0.5, 1, 2, 3

3. Results and discussion

3.1. Validation results

Robust transfers start with validated methods. It is consequently very important to be sure of the acceptability of the considered analytical procedure. With this intention, the validation results obtained by the sending site were treated according to the recent approach based on the accuracy profile [7,8]. In order to validate the method, three series of experiments with three repetitions at five concentration levels ranging from 40 to 120 μg/ml for fenofibrate and ranging from 880 to 1600 ng/ml for fenofibric acid were executed. Considering that the objective of the method was to determine an active compound in a drug product and its main impurity, the acceptance limits were set at 5 and 10% for fenofibrate and fenofibric acid, respectively. The validation results for fenofibrate and fenofibric acid are presented in Table 2(a) and (b).

The accuracy profiles, used as decision tools to assess the validity of a method, are constructed from the total error (bias + standard deviation) of the procedure. They are obtained by computing, for each concentration level, the β-expectation tolerance interval that allows evaluating the proportion of expected measurements that will fall inside the acceptance limits in the future use of the analytical method [9]. The accuracy profiles obtained for these two analytes are presented in Fig. 1(a) and (b).

As shown in Fig. 1(a) and (b), the tolerance limits remained within the acceptance limits on the whole concentration range investigated for both analytes. Therefore, this method was found valid; we could then consider its transfer.

3.2. Simulations and experimental design

To determine the adequate experimental design, two series of simulations of transfer were carried out. The first series was carried out with R.S.D. of repeatability and intermediate precision both set at 0.5%. For the second series, these R.S.D. were both fixed at 1.0%. The proportion β of all the samples contained in the β-expectation tolerance interval was fixed at 0.90. In other words, this means that at least 90% of future individual results are expected to lie within this interval. The simulations were carried out for one series for the sending laboratory and four different combinations of numbers of series and repetitions with regard to the receiving laboratory. For each of these simulations, the approach by the total error was used to analyze the data and the probabilities of showing acceptance of the transfer were calculated. The results obtained are presented in Tables 3 and 4.

Table 3 shows that, with regard to the transfer of this analytical method, it is possible to conclude correctly about the validity of the transfer by carrying out only one series at the sending laboratory and by realizing three series at the receiving laboratory, for a number of repetitions per series fixed at three. Indeed, for an acceptance limit fixed at 5% and for 3 series, the probability of accepting the transfer when the bias is acceptable is close to 100% as shown in Table 3. The same conclusion can be made for the 10% acceptance limit.

Table 2
Validation results for (a) fenofibrate and (b) fenofibric acid

(a) Validation criterion for fenofibrate

Response function ($k=3$; $n=6$)	Linear regression through 0		
	Series 1:	Series 2:	Series 3:
Slope	180.4	180.6	180.6
Trueness ($k=3$; $n=6$)			
Relative bias (%)			
40 μg/ml		0.4	
60 μg/ml		0.5	
80 μg/ml		0.2	
100 μg/ml		0.4	
120 μg/ml		0.1	
Precision ($k=3$; $n=6$)			
Repeatability/intermediate precision (R.S.D.%)			
40 μg/ml		0.63/0.63	
60 μg/ml		0.34/0.34	
80 μg/ml		0.51/0.53	
100 μg/ml		0.1/0.17	
120 μg/ml		0.26/0.26	
Accuracy ($k=3$; $n=6$)			
β-expectation tolerance limits of the relative error (%)			
40 μg/ml		[−1.0, 1.8]	
60 μg/ml		[−0.4, 1.3]	
80 μg/ml		[−1,1.3]	
100 μg/ml		[−0.2,1.0]	
120 μg/ml		[−0.5, 0.7]	
Linearity ($k=3$; $n=6$)			
Range (μg/ml)		[40, 120]	
Slope		0.9996	
Intercrept		0.2138	
r^2		0.9999	
LOD (μg/ml)		0.92	
LOQ (μg/ml)		40	

(b) Validation criterion for fenofibric acid

Response function ($k=3$; $n=6$)	Linear regression through 0		
	Series 1:	Series 2:	Series 3:
Slope	0.1644	0.1648	0.1633
Trueness ($k=3$; $n=6$)			
Relative bias (%)			
80 ng/ml		0.6	
200 ng/ml		−0.4	
400 ng/ml		0.5	
800 ng/ml		0.1	
1600 ng/ml		0.8	
Precision ($k=3$; $n=6$)			
Repeatability/intermediate precision (R.S.D.%)			
80 ng/ml		1.34/1.34	
200 ng/ml		0.66/0.75	
400 ng/ml		0.82/1.04	
800 ng/ml		0.63/1.04	
1600 ng/ml		0.41/0.91	
Accuracy ($k=3$; $n=6$)			
β-expectation tolerance limits of the relative error (%)			
80 ng/ml		[−2.3, 3.5]	
200 ng/ml		[−2.4, 1.6]	

Table 2 (*Continued*)

(b) Validation criterion for fenofibric acid

Response function ($k=3$; $n=6$)	Linear regression through 0		
	Series 1:	Series 2:	Series 3:
Slope	0.1644	0.1648	0.1633
400 ng/ml		[−2.2,3.1]	
800 ng/ml		[−3.4, 3.5]	
1600 ng/ml		[−2.6,4.1]	
Linearity ($k=3$; $n=6$)			
Range (ng/ml)		[80, 1600]	
Slope		1.008	
Intercrept		−1.528	
r^2		0.9999	
LOD (ng/ml)		8.66	
LOQ (ng/ml)		80	

Table 4 shows that the probability to conclude correctly that the transfer is acceptable is also very high, for an acceptance limit of 10% and the realization of 3 series. However, when the acceptance limit is set at 5%, Table 4 shows that by increasing

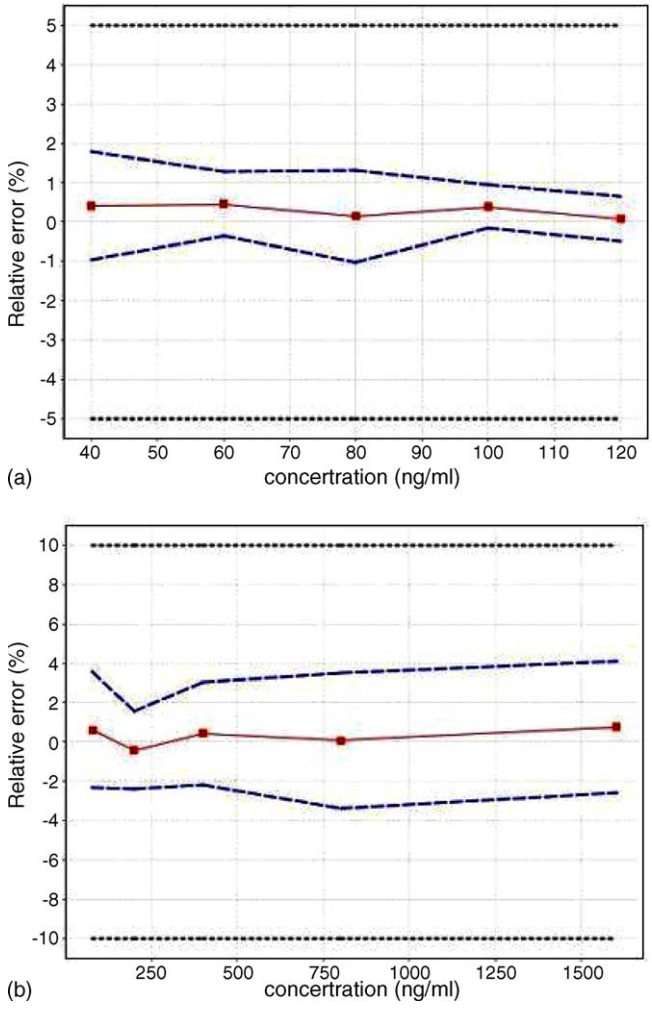

Fig. 1. Fenofibrate (a) and fenofibric acid (b) accuracy profile: continuous line is the relative bias; dashed line the tolerance interval; and dotted line the acceptance limits set at 5% for fenofibrate and 10% for fenofibric acid.

Table 3
Simulated probabilities of concluding that the transfer is acceptable with $R.S.D._{REP} = 0.5\%$, $R.S.D._{IP} = 0.5\%$ and $\beta = 0.90$

	3 Series		5 Series		7 Series		9 Series	
	5[a]	10[a]	5[a]	10[a]	5[a]	10[a]	5[a]	10[a]
True bias (%)								
0	100	100	100	100	100	100	100	100
0.5	100	100	100	100	100	100	100	100
1	100	100	100	100	100	100	100	100
2	99.9	100	100	100	100	100	100	100
3	97.8	100	99.5	100	99.6	100	100	100

The number of repetitions per series is set to 3.
[a] Acceptance limits (%).

Table 4
Simulated probabilities of concluding that the transfer is acceptable with $R.S.D._{REP} = 1.0\%$, $R.S.D._{IP} = 1.0\%$ and $\beta = 0.90$

	3 Series		5 Series		7 Series		9 Series	
	5[a]	10[a]	5[a]	10[a]	5[a]	10[a]	5[a]	10[a]
True bias (%)								
0	84.3	100	92.6	100	94.3	100	96.2	100
0.5	80	100	91.3	100	93.6	100	94.9	100
1	76.6	99.8	87.9	100	91.6	100	91.8	100
2	57.5	100	68.1	100	74.1	100	75.1	100
3	38.2	99.8	45.4	100	47.7	100	51.2	100

The number of repetitions per series is set to 3.
[a] Acceptance limits (%).

the number of series from 3 to 5, the probability of accepting the transfer is significantly improved. Therefore, in order to obtain a better estimate of the inter-series variances of the receiving laboratory and to follow the recommendations of the literature [4,5], 5 series of experiments were made at the receiving laboratory. As required by the analytical procedure, each sample is injected three times. Table 5 summarizes the experimental design established.

Table 5
Experimental design used for the evaluation of the method transfer

Series	Sender	Receiver				
	1	1	2	3	4	5
# Repetitions per series	3	3	3	3	3	3
# Injections per repetitions	3	3	3	3	3	3
Operator	A	B	C	B	C	B
HPLC equipment	I	II	II	III	III	III

The batch of Fénogal® used to carry out the transfer was not containing fenofibric acid. Therefore, as recommended in the ISPE guide [2], a known quantity of this breakdown product was added in each sample in order to make sure that the receiving laboratory was also able to quantify it. During the samples preparation (cf. Section 2.5), 4.0 ml of standard solution of fenofibric acid were introduced before adding the phosphate buffer/methanol mixture. The theoretical concentration of fenofibric acid in the samples is 80 ng/ml. This concentration corresponds to the maximum tolerated content (0.1%) and to the limit of quantitation for fenofibric acid determined at the analytical method validation step in the sending site.

3.3. Statistical analysis of the results

3.3.1. Conventional statistical approaches

The results obtained with the conventional statistical approaches are included in Table 6(a) and (b) for fenofibrate and fenofibric acid, respectively. The conclusions concerning the acceptability of the transfer towards the receiving laboratory is also presented in these tables. The acceptance limits for fenofibrate were set at 2 and 3% for the precision and trueness criterions respectively. For fenofibric acid, they were set at 10% for precision and 30% for trueness. As shown in Table 6(a) and (b), the transfer was accepted by all conventional approaches except by the equivalence approach for the precision criterion for both analytes.

Table 6
Summary of the results obtained with the conventional statistical approaches during the transfer of the method of determination of (a) fenofibrate and (b) fenofibric acid

Estimated parameter	Statistical approach and corresponding result		Acceptation of transfer
(a) Fenofibrate			
Precision	Descriptive approach	$R.S.D._{IP,R} = 1.46\%$	Yes
	Equivalence test	$L_{U,R.S.D.} = 4.06\%$	No
Trueness	Descriptive approach	Bias = −0.79%	Yes
	Difference test	Cl (95%) = [−1.95%; +0.38%]	Yes
	Equivalence test	Cl (90) = [−1.71%;+0.14%]	Yes
(b) Fenofibric acid			
Precision	Descriptive approach	$R.S.D._{IP,R} = 4.43\%$	Yes
	Equivalence test	$L_{U,R.S.D.} = 10.12\%$	No
Trueness	Descriptive approach	Bias = 3.02%	Yes
	Difference test	Cl (95%) = (−3.98%; +10.02%)	Yes
	Equivalence test	Cl (90%) = (−2.47%; +8.51%)	Yes

$R.S.D._{IP,R}$: receiving laboratory relative standard deviation for intermediate precision; $L_{U,R.S.D.}$: receiving laboratory upper confidence limit of the $R.S.D._{IPR,R}$; Cl: confidence interval of the relative bias at significant level of 5 and 10%.

Table 7
Results for the transfer of the analytical method obtained from the Tolerance Interval and the Risk approaches

	Fenofibrate	Fenofibric acid
Tolerance Interval approach		
Acceptance limits (±λ%)	[95; 105]	[90; 110]
Decision interval (%)	[95.7; 102.7]	[90.3; 110.1]
Risk approach		
Maximum risk ($1-\beta$) (%)	10	10
Effective risk P (%)	1.9	6.6

The decision based on the Descriptive approaches only compares the estimated values of the R.S.D.$_{IP}$ of the receiver and of the relative bias to their respective acceptance limits, therefore not controlling any of the producer or consumer risks (type I or II errors). The Difference approach will accept the transfer if the 0% value is included in the two-sided 95% confidence interval of the relative bias. Transfer with high variability will always be accepted and those with a bias and a small variability rejected. This problem is similar to the one encountered in validation or bioequivalence [10,11] and shows the inadequacy of this approach to demonstrate equivalence of results. Both the Descriptive and the Difference approaches should therefore be banished to assess the validity of an analytical method transfer.

The Equivalence approach rejected the transfer for the precision criterion for fenofibrate and fenofibric acid as the upper confidence limit of the relative standard deviation for intermediate precision ($L_{U,R.S.D.}$) was exceeding the acceptance limits. This approach corrects the inconsistencies of the two previous ones but still does not allow the compensation of a high random error by a small systematic one or vice versa. Furthermore this approach does not give information on the future behavior of the analytical method and therefore no guarantees are available at the end of the transfer that the receiver will master the method.

3.3.2. New statistical approaches

The innovation of these new statistical approaches is to use the total error of the results of the transfer as decision tool. For these approaches, the decision criterion is consequently made by simultaneously grouping the trueness and the precision under the notion of accuracy [7,12,13]. In this context, the decision rule for the Tolerance Interval approach consists in the integration of the tolerance interval within the acceptance limits previously defined according to the intended use of the analytical procedure evaluated. Whereas for the Risk approach, the probability of having results outside the acceptance limits is compared to a maximum pre-specified risk $1-\beta$.

The acceptance limits λ for fenofibrate and fenofibric acid were set at 5 and 10%, respectively, according to regulations. The maximum risk tolerated $1-\beta$ was fixed at 10% for each analyte. Table 7 shows the results of the transfer for each compound with both statistical approaches.

In order to evaluate the characteristics of these new approaches, they have been compared with the three already described in the literature, namely the descriptive approach, the difference approach and the equivalence approach.

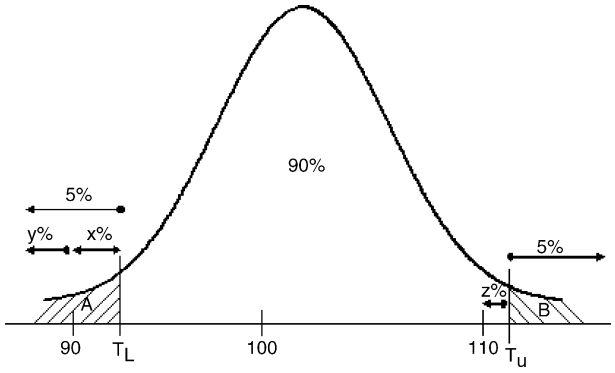

Fig. 2. Difference between the Tolerance Interval and the Risk approach for the transfer results of fenofibric acid. T_L is the lower limit of the tolerance interval and T_U the upper limit of the tolerance interval.

For fenofibrate both approaches accepted the transfer of the analytical method to the receiving laboratory. Indeed, the tolerance interval is included in the acceptance limits and the effective risk P is smaller than the maximum tolerated risk ($1-\beta$). From these results and for the tolerance approach at least 90% of the future results of fenofibrate obtained with this analytical procedure will lay at maximum 5% of the nominal value of fenofibrate. Furthermore, the Risk approach gives the risk of having future results of fenofibrate outside the 5% acceptance limits. This risk is very low for fenofibrate, reaching only 1.9%.

For fenofibric acid, the transfer is accepted with the Risk approach but not with the Tolerance Interval approach. Here, the tolerance interval steps outside the acceptance limits whereas the effective risk is smaller than the maximum tolerated risk of 10%, reaching only 6.6%. This situation is explained in Fig. 2.

Ninety percent of the future results of the receiving laboratory are inside the tolerance interval [T_L; T_U]. As this interval is a two-sided β-expectation tolerance interval, 5% of future results are outside the upper limit of this tolerance interval (region B in Fig. 2) as well as 5% are outside the lower limit of this interval (region A in Fig. 2). As shown in Fig. 2 the upper limit of the tolerance interval is outside the pre-specified upper acceptance limit, therefore more than 5% of the results will lay outside this limit: $(5+z)$%. However, the lower limit of the tolerance interval is well inside the lower acceptance limit, therefore less than 5% of future results are outside this acceptance limit: $y(\%) = 5 - x$, which compensate the higher proportion of results outside the upper acceptance limit ($x\% > z\%$). In fine more than 90% of future results are inside the acceptance limits: 93.4%. The Tolerance Interval approach should accept the transfer as at least 90% of future results are within the acceptance limits which fulfills its requirements. However it does not. The Risk approach is therefore more powerful than the Tolerance Interval approach. This explains the results of Dewé et al. [5] who also observed in their simulations that the Risk approach had more power than the Tolerance Interval one.

The objective of any quantitative analytical procedure is to obtain each of its results close enough to the true value of the measured quantity [8]. Therefore, the objective of an analytical

method transfer must be to give guarantees to laboratories and regulatory bodies that each future measurements made by the receiving laboratory will be close enough to the true value of the analyte in the samples. Only the two total error approaches fulfilled this objective. Furthermore, in the current framework of the process analytical technology (PAT) launched by the FDA [14] these approaches strictly control the consumer risk and allow the management of the risk of having out of specifications measurements by giving an estimation of this last risk.

4. Conclusion

The objective of an analytical method transfer is to provide users guarantees in order to minimize the risks to have future results out of specifications.

The total error approaches achieve this by: (1) providing guarantees that at least 90% of future individual results will be inside the specified acceptance limits for the Tolerance Interval approach; or (2) by computing the risk of having future individual results outside the acceptance limits for the Risk approach. The conventional statistical approaches do not fulfill this and they should be avoided in assessing the validity of a transfer.

These two new approaches were applied to the transfer of a LC method for the quantitative determination of an active substance, fenofibrate, and its principal degradation product, fenofibric acid, from its development site to its routine use site. The Risk approach appeared to be the most suitable one. This total error approach gave the guarantee that the receiver masters the analytical method and furthermore allowed managing the risks of having results out of specifications during routine use.

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