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Harmonization of strategies for the validation of quantitative analytical procedures
A SFSTP proposal—part I

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Abstract

This paper is the first part of a summary report of a new commission of the Société Française des Sciences et Techniques Pharmaceutiques (SFSTP). The main objective of this commission was the harmonization of approaches for the validation of quantitative analytical procedures. Indeed, the principle of the validation of theses procedures is today widely spread in all the domains of activities where measurements are made. Nevertheless, this simple question of acceptability or not of an analytical procedure for a given application, remains incompletely determined in several cases despite the various regulations relating to the good practices (GLP, GMP, . . .) and other documents of normative character (ISO, ICH, FDA, . . .). There are many official documents describing the criteria of validation to be tested, but they do not propose any experimental protocol and limit themselves most often to the general concepts. For those reasons, two previous SFSTP commissions elaborated validation guides to concretely help the industrial scientists in charge of drug development to apply those regulatory recommendations. If these two first guides widely contributed to the use and progress of analytical validations, they present, nevertheless, weaknesses regarding the conclusions of the performed statistical tests and the decisions to be made with respect to the acceptance limits defined by the use of an analytical procedure. The present paper proposes to review even the bases of the analytical validation for developing harmonized approach, by distinguishing notably the diagnosis rules and the decision rules. This latter rule is based on the use of the accuracy profile, uses the notion of total error and allows to simplify the approach of the validation of an analytical procedure while checking the associated risk to its usage. Thanks to this novel validation approach, it is possible to unambiguously demonstrate the fitness for purpose of a new method as stated in all regulatory documents.

Keywords: Analytical procedure; Validation; Harmonization; β-Expectation tolerance interval; Quantitative analysis

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1. Introduction

The present paper is the first part of a summary report resulting from a new Société Française des Sciences et Techniques Pharmaceutiques (SFSTP) Commission on the harmonization of approaches for the validation of quantitative analytical procedures. The whole report has been published in the French journal of the SFSTP [1]. The different sectors aimed by this commission report are: (1) the corporation's contractors of services; (2) the regulatory bodies; (3) the official quality laboratories; and (4) the industries of various sectors, namely chemistry, pharmacy, bio-pharmacy, food processing, environment, cosmetology, etc. The main references of the SFSTP commission report are: (1) regulatory bodies documents [2–11]; (2) ICH documents (Q2A and Q2B) [5,6]; (3) FDA documents (guidance for industry) [5,6,10,11]; (4) ISO documents [12–16] especially 5725 (AFNOR X06-041) document [13] and ISO 17025 document [14]; and (5) Commission Decision 2002/657/EEC (SANCO) [17].

As can be seen in the bibliography, the validation of the assay procedures is a vast subject that interests the scientific and regulatory worlds since many years [1–45]. Among these documents, the following documents were also used to support the present guide: (1) SFSTP '92 guide [20], SFSTP '97 guide [21,22] and publications related to the Conference of Washington (1990) [11,18,19,21,22].

The different regulations concerning to the good practices (GLP, GMP, GCP, and others) as well as the normative or regulatory documents (ISO, ICH, EMEA, and FDA) suggest that all procedures have to comply with acceptance criteria. This request imposes, therefore, that these procedures must be validated. There are several documents defining the validation criteria to be tested, but they do not propose experimental approaches and limit themselves, most often, to the general concepts. It is why the members o the SFSTP have contributed to the elaboration of consensus validation guides to help the pharmaceutical industry to validate their analytical procedures (pharmaceutical specialties) [20] and bio-pharmaceutical procedures (procedures implied in pharmacokinetics and bioequivalence studies) [21], respectively.

Today, one can say that these two guides have significantly contributed to make progress the validation of the analytical procedures. Nevertheless, the first guide (SFSTP '92) [20] has been considered to be too exclusively dedicated to the pharmaceutical specialties and has showed weaknesses regarding the objective of the validation. For example, the analyst could be penalized when its method was too precise. In addition, he was confronted to a lot of statistical tests generally complicating his decision rather than helping him. This paradoxical situation comes from the confusion between the diagnosis rules and decision rules. Same confusion could be observed in the second validation guide (SFSTP '97) [21] devoted to bio-analytical procedures. However, the first bases of accuracy profile was proposed in the second guide. This concept could be extended to other activity sectors such as environment or food analysis but that document was only dedicated to biopharmaceutical analysis [22,44].

For these different reasons, the goal of the new SFSTP document [1] is mainly to reconcile the objectives of the validation with those of the analytical procedure. It also aims to provide a simple decision tool based on the total error (bias + standard deviation) of the procedure. This approach allows to considerably minimize the risk to accept a procedure that would not be sufficiently accurate or, to the opposite, to reject a procedure that would be capable. Concurrently to these general concepts, the others objectives of the new SFSTP guide are to propose a consensus on the norms usually recognized, while widely incorporating the ISO terminology, and to insist on the validation of the analytical procedure in the same way as it will be used in routine. It also presents experimental strategies for the validation of quantitative procedures, regardless of the industrial sector, to optimally use experiments performed, to extract a maximum of information from the results and to minimize in routine the risks to re-analyze samples. Since it is impossible to synthesize this important work in a single document, the present paper is limited to general concepts and the experimental strategies will be presented in a second paper [46].

2. Objectives of an analytical procedure

In order to specify the objectives of the validation, it is necessary to go back to the nature itself of an analytical method. Is its objective to demonstrate that the response varies linearly as a function of the concentration, that the bias and the precision are less than x% or rather to quantify as accurately as possible each unknown quantity? These interrogations seem to be the questions of interest. The objective of a "*good*" analytical procedure is to be able to quantify as accurately as possible each of the unknown quantities that the laboratory will have to determine [38–40]. In other words, what the analyst is seeking is that the difference between the "*measured value*" (x) and the "*true value*" (μ_T), which will always remain unknown, is as low as possible or at least lower than an acceptable limit. This requirement can be expressed as follows:

$$-\lambda < x - \mu_T < \lambda \Leftrightarrow |x - \mu_T| < \lambda \quad (1)$$

with λ, the acceptance limit which can be different depending on the requirements of the analyst or the objective of the analytical procedure. Indeed, the acceptance limit can vary according to the intended use of the analytical method (e.g. 1%–2% for the analysis of a bulk pharmaceutical compounds, 5% for the determination of active ingredients in dosage forms, 15% in bioanalysis, etc.). Important concepts are thus introduced, not only acceptance limits for the performance of an analytical method but also the responsibility that the analyst has to take in the decision of accepting the performance of the method with respect to its intended use.

On the other hand, every analytical method can be characterized by a systematic error or "*true bias*" μ_M and a random error or "*true variance*" σ_M^2 (measured by a standard deviation). Both these parameters are inherent of each analytical method and they are also always unknown as well as the "*true value*" μ_T of the sample to be determined [38]. In fact, an estimation of the method bias and variance can be obtained from the experiments carried out during method validation. The reliability of these estimates depends on the adequacy of the measurements performed on known samples, called validation standards (SV), the experimental design and the number of replicates during the validation phase. However, these estimates of bias and variance are not objectives per se. It is an intermediary but obligatory steps to evaluate the ability of the analytical procedure to quantify with a sufficient accuracy each of the unknown quantities, i.e. to fulfil its objective [38,39]. On the basis of these estimates for bias and variance, the acceptance limits for the performance of the method, it is possible to define the concept of "*good analytical method*" for a given field (e.g. biopharmaceutical analysis).

Fig. 1 illustrates graphically those concepts as well as Eq. (1). This figure represents the distribution of 95% of the measurements given by four different hypothetical–analytical procedures having each a "*true bias*" μ_M and a "*true precision*" σ_M^2 as well as a common acceptance limit λ. In this figure, the relative acceptance limits λ are set $\pm$15%, a classical choice for bioanalytical procedures [11,18,19,21,34]. Which are the procedures that fulfil this objective and which ones will the analyst retain as valid?

As illustrated in Fig. 1, the procedure 3 (0% of bias, 20% precision; R.S.D., %) does not satisfy its objective since too many measures are obtained beyond +15% or −15% of the true value of the samples. This procedure is characterized by a bias null but shows an unsatisfactory precision (R.S.D., 20%). In the same way, procedure 4 does not fulfil its objective either. The proportion of measures obtained outside the acceptance limits is also too important. Note nevertheless that the procedure 4 is characterized by a bias (+7%) and a precision (R.S.D., 12%) that are each inferior to 15% as required by the Washington conference for the bioanalytical methods [10,32]. In contrast, procedures 1 and 2 meet the fixed objectives. They can be, thus, declared as valid procedures. Indeed, with these two procedures, the analyst has the guarantee that at least 95% and 80%, respectively, of the results will be inside the acceptance limits. Procedure 1 presents a bias (+7%), but is, however, very precise (R.S.D., 3%). On the other hand, procedure 2 is characterized by a negligible bias (+1%), but is less precise (R.S.D., 10%). The differences between these two procedures do not matter since in both cases the results obtained are never too far from true values of the sample to quantify, i.e. within the acceptance limits. Consequently, the quality of the results is more important than the intrinsic characteristic properties of the procedure in terms of bias or precision [38,39,44].

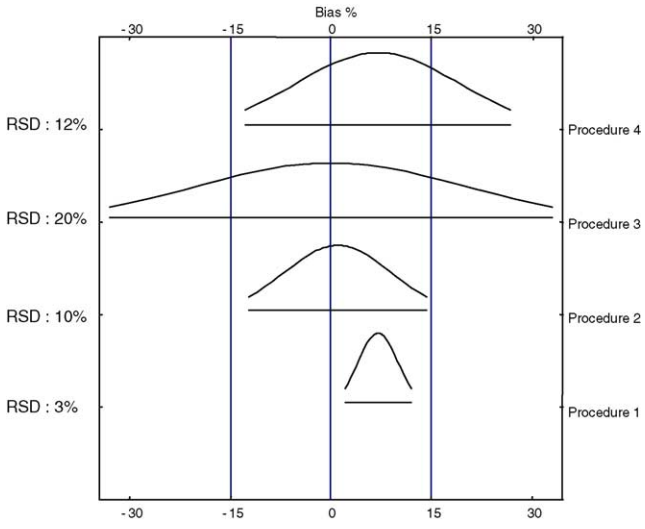

Fig. 1. Examples of procedures having the same acceptance limits, λ = $\pm$15%. The bias is expressed in percent of difference to the true value and the precision as a coefficient of variation.

Aiming to develop a procedure without bias and without error has a considerable cost. This target is unrealistic for an analyst who has generally only little time to systematically and meticulously optimize all the analytical parameters in the development phase even if the use of experimental design is recommended and well described in the literature [6,47–50]. To overcome this dilemma, the analyst will have to take minimal risks (or all at least compatible with the analytical objectives). To control this risk, the reasoning can be reversed and one can fix as starting assumption that only an acceptable maximum proportion of future measures will be outside the acceptance limits, e.g. 5% of the measurements or 20% of the measurements to the maximum outside the acceptance limits. This proportion represents, therefore, the maximum risk that the analyst is ready to take.

As shown in Fig. 2, another possible illustration consists in representing the domain of acceptable analytical procedures, acceptance region, being characterized by a "*true bias*" μ_M and a "*true precision*" σ_M^2 as a function of a maximum risk chosen. Inside triangles, acceptable procedures are those for which a given proportion of measurements, i.e. 95%, 80% or 66%, are likely to fall within the $\pm$15% acceptance limits (in this example, following recommendations of Washington conference) [11,18]. Therefore, it is in these domains that the "*good analytical procedure*" is located with respect to the proportion of measurements that the analyst would like to have within acceptance limits. The triangles correspond to proportions of 95%, 80%, and 66% of measurements included within the fixed acceptance limits. The proportion desired will obviously depend of the objectives of the analytical procedure. In Fig. 2, the interior triangle represents the area of all the analytical procedures for which the analyst wish that 95 times out of 100, the result x be included within the acceptance limits set by him according to the constraints of his activity sector (pharmaceutical, environment or food analysis).

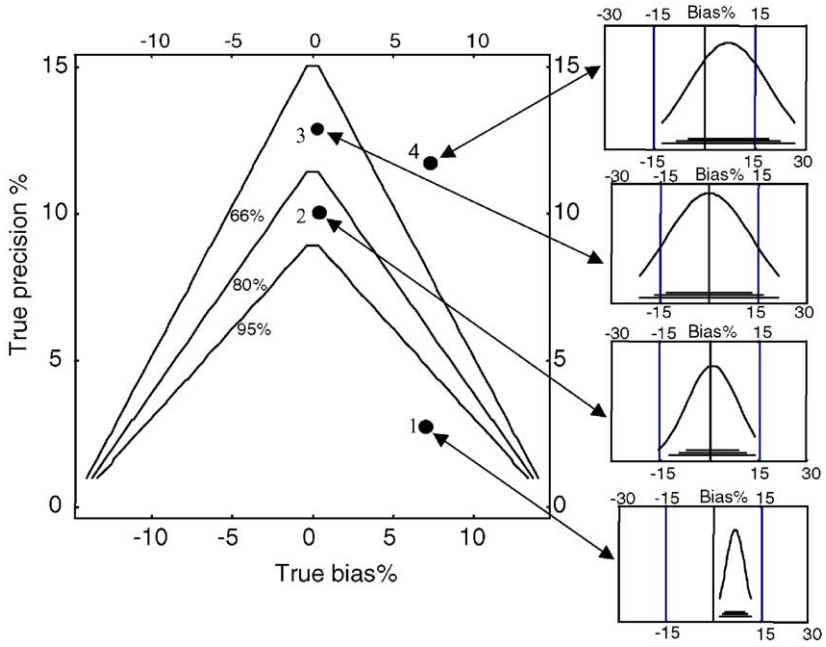

Fig. 2. Acceptance limits of the performances of an analytical procedure according to its "*true bias*" (%) and its "*true precision*" (CV, %).

Fig. 2 shows also two other triangles corresponding to proportions of 80% and 66%, respectively, of the measurements included within the limits of acceptance. The proportion of 80% is only given for information and do not correspond to any known regulatory requirement. However, it is important to realize that for a procedure characterized by a null true bias and a true precision of 15%, only about 66% of the measurements will fall within the acceptance limits. This proportion reaches 95% when the precision improves to 8%, still with a null bias. In fact, the proportion of 66% refers to the 4/6/15 rule recommended by the Conference of Washington (1990) for the quality control (QC) samples in routine analysis [11,18]. Indeed, that rule states that at least four quality control out of six must fall within the acceptance limits of ±15% [10,32]. This decision rule is equivalent to accept that only two-thirds or 66% measurements are within the acceptance limits. Consequently, Fig. 2 clearly illustrates the gap existing between requirements in validation phase and those required in routine to guarantee the quality of the results. This gap is paradoxical since the goal of the validation of an analytical procedure is to demonstrate that the analytical procedure will be able to fulfil its intended objectives in routine analysis [44].

For illustrative purpose, the four procedures illustrated in Fig. 1 (1–4) have been inserted in Fig. 2 according to their respective performances in terms of bias and precision. It can be thus observed that procedures 1 and 2 are located inside of the acceptance region that guarantees that at least 95% and 80%, respectively, of the results will be within the acceptance limits. On the other hand, for the same risk of the measurements outside of the acceptance limits, procedures 3 and 4 are not considered as valid.

A procedure can be qualified as acceptable if it is very likely, i.e. with a "*guarantee*", that the difference between every measurement (x) of a sample and its "*true value*" (μ_T) is inside the acceptance limits predefined by the analyst. This concept can be described by the following expression:

$$P(|x - \mu_T| < \lambda) \geq \beta \quad (2)$$

with β the proportion of measurements inside the acceptance limits and λ the acceptance limits fixed a priori by the analyst according to the objectives of the method. The expected proportion of measures falling outside the acceptance limits evaluates the risk of an analytical procedure.

3. Objective of the validation

Knowing that the characteristics of "*true bias*" and of "*true precision*" are parameters that will always remain unknown but that will be estimated by the measurements obtained in validation phase, what is the objective of validation?

Under these conditions, it seems reasonable to claim that the objective of validation is to give to the laboratories as well as to regulatory bodies "*guarantees*" that every single measure that will be later performed in routine analysis will be "*close enough*" to the unknown "*true value*" of the sample to be analysed or at least that the difference will be lower than an acceptable limit taking into account the intended use of the method. The goals of the validation are thus to minimize the consumer risk as well as the producer risk [51]. Consequently, the objective of the validation cannot be simply limited to obtaining estimates of bias and variance but must be focused on the evaluation of

the risk even if these estimators are needed to evaluate the risk.

With respect to this objective, two basic notions mentioned above have to be explained:

"*close enough*", meaning, for example, that the realized measure in routine will be to less than *x*% (*x* retrieves itself to the acceptance limit λ) of his "*true value*" unknown (cf. Eq. (1));
"*guarantees*", meaning that it is very likely that whatever the measure, it will be "close enough" from the "*true value*" unknown (cf. Eq. (2)).

In that respect, trueness, precision, linearity, ... are no more "statistics" allowing to quantify these guarantees. In fact, one expects from an analytical procedure to be able to quantify and not to be precise, even if the precision itself unquestionably increases the likelihood to be successful. In this perspective, it is necessary to differentiate the statistics which allow to make a *decision* (e.g. the procedure can be considered as valid or not on the basis of its aptitude to quantify) and those which help to make a *diagnosis* (e.g. statistical tests evaluating the adequacy of the regression model or the homogeneity of the variances).

In fact, adapted decision tools are really needed to give guarantees that any future measurements will be reasonably inside the acceptance limits. If the guarantees offered by the decision rule are not satisfactory, then the diagnosis tools will help the analyst to identify the possible causes of the problem; but only if the guarantees are not satisfied [38–40].

4. Decision rules

The examination of the current situation with respect to the decision rules used in the validation phase [20,21] shows that the most of them are based on the use of the null hypothesis as follows.

$$H_0 : \text{bias} = 0 \leftrightarrow H_0 : \text{relative bias} = 0\% \leftrightarrow H_0 : \text{recovery} = 100\% \quad (3)$$

with the bias = $x - \mu_T$, the relative bias = $(x - \mu_T/\mu_T) \times 100$ and the recovery = $(x/\mu_T) \times 100$.

On this basis, a procedure is wrongly declared adequate when the 95% confidence interval of the average bias includes the value of 0 (0% and 100% in the case of the relative bias and recovery, respectively). However, this test is inadequate in the validation context of analytical procedures because the decision is based on the computation of the rejection criterion of the Student's *t*-test. In order to illustrate this practice, four procedures are presented in Fig. 3A as example. It is the same hypothetical procedures illustrated in Fig. 1 and for which the interval represents 95% of the measures expected.

According to the decision rule described in Eq. (3), procedures 2, 3, and 4 can be declared as valid while procedure 1 is rejected. Nevertheless, a more attentive examination shows that:

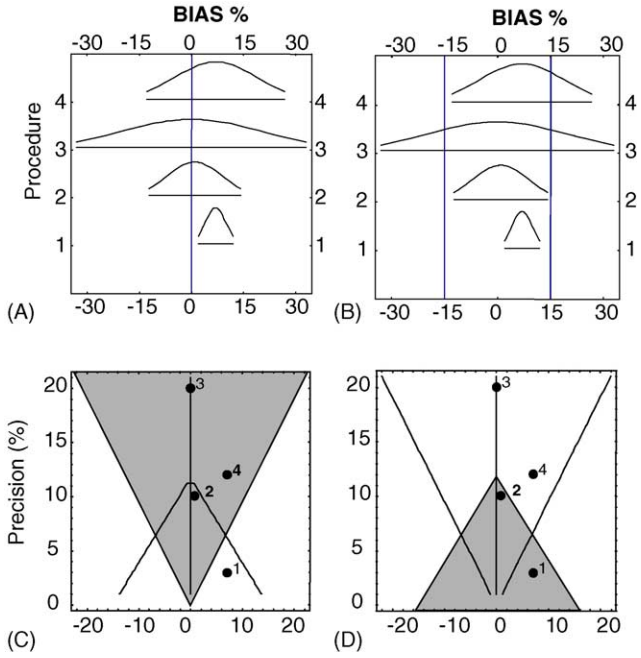

Fig. 3. Illustration of the decision rules. (A) and (C) Test based on the null hypothesis H_0: bias = 0; (B) and (D) test based on the acceptance limits of a procedure.

procedure 1 presents a reduced bias (+7%) and a small dispersion of the measures (3% CV); this procedure is, however, rejected by this rule;
procedure 3 is characterized by a large dispersion of the measures (20% CV);
procedure 4 has a bias equal to that of procedure 1 (7%), but a dispersion of measures about four times superior. However, procedure 4 is considered as valid but not procedure 1.

These two last contradictions can be explained as follows:

The greater the variance, i.e. the worse the precision, then the more likely the confidence interval to contain the 0 bias value, and thus, the procedure to be declared as valid.
The smaller the variance, i.e. the better the precision, then the more likely it is that the confidence interval to not contain the 0 bias value, leading to reject the procedure.

This paradoxical situation which is obviously not the objective desired is illustrated in Fig. 3A showing how the validity of the four procedures is accepted or rejected. On contrary, as can be seen from Fig. 3B, working with an acceptance limit (±λ) defined according to the objectives of the procedure allows overcoming this contradiction. The four procedures represented are the same that those of Fig. 3A, only the decision rule changes, as illustrated by the two vertical traits at ± 15%. With this rule, the procedures 1 and 2 are considered as valid while procedures 3 and 4 are rejected because they provide too many results outside the acceptance limits.

Fig. 3C represents in gray the region (bias, precision) of the procedures that will be considered as valid by the use of the null hypothesis. Some procedures characterized by a significant bias and a poor precision are located inside this acceptance region while other procedures with a similar bias and a better precision are rejected. The use of the null hypothesis test is, therefore, inadequate in the framework of the validation of analytical procedures.

Fig. 3D represents in gray the region of the procedures that will be accepted as valid by the use of acceptance limits. In this case, the triangle corresponds to the set of procedures for which the proportion of the measures inside the acceptance limits is greater or equal to the proportion chosen a priori (e.g. 80%), such as described in Eq. (2). This latter decision rule appears clearly more sensible than the previous one based on the null hypothesis since all procedures having a small dispersion of the measurements are accepted, while the procedures having a large variance are rejected. In addition, if a procedure has a bias, it should have a small variance to be accepted. Symmetrically, a procedure with a high variance should have a small bias to be accepted.

Note that the use of the null hypothesis, illustrated in Fig. 3C, is still widely used in many cases, such as the test of null intercept, of equality of slopes, lack of fit, etc. [20,21,35]. With all these statistical tests, the less the procedure is precise, the more chance to pass successfully these tests. This situation is certainly not the one expected by the analyst using the statistics to evaluate the capability of the method under investigation. In this context, the decision rule, easy and visual, consists in the use of the accuracy profile with relative acceptance limits (±λ) [22,38–41,44]. As illustrated in Fig. 4, the accuracy profile, constructed from the confidence intervals on the expected measures, allows to decide the capability or not of an analytical procedure to give results inside acceptance limits.

The area in gray describes the range in which the procedure is able to quantify with a known accuracy and a risk fixed a priori by the analyst. If the analyst is ready to assume, for example a risk of 5%, he will be able at the end of the validation of his procedure to guarantee that 95 times out of 100 the future measures given by his procedure will be included within the acceptance limits fixed according to the regulatory requirements (e.g.: 1% or 2% on bulk, 5% on pharmaceutical specialties, 15% in bioanalysis, environment, etc.). Since the "*true bias*" and the "*true precision*" of an analytical procedure are unknown, the accuracy profile (Fig. 4) by concentration level (C1, C2, ...) is obtained by computing the confidence interval that allows to evaluate the proportion of expected measures inside the acceptance limits (±λ). This profile is constructed from the available estimates of the bias and precision of the analytical procedure at each concentration level at the end of the validation phase. This confidence interval is the so-called "*β-expectation tolerance interval*" [52]. It defines an interval where the expected proportion of future results will fall in β. This tolerance interval obeys to the following property:

$$E_{\hat{\mu},\hat{\sigma}}\{P[|x_i - \mu_T| < \lambda]/\hat{\mu}_M, \hat{\sigma}_M\} \geq \beta \quad (4)$$

with E meaning "*expected value*" of the result. The calculation of the "*β-expectation tolerance interval*" requires estimates of the bias and the standard deviation of intermediate precision of the method, respectively, noted $\hat{\mu}_M$, $\hat{\sigma}_M$.

Eq. (4) is illustrated by Fig. 5. The distribution not shadowed represents the true distribution (unknown) of the procedure under validation. The gray area represents the expected probability that a measure will fall within –15% and +15% on the basis of the observed distribution of the method characterized by estimated bias and precision in validation phase. It can also be observed from Fig. 5 that the estimated bias and precision of the procedure are different of the "*true bias*" and "*true precision*". However, if the estimates of the bias and variance (cf. Eq. (4)) are essential elements to compute the evaluation of the expected proportion of measures within acceptance limits, the decision is not made on those estimates of bias and variance. The practical use of Eq. (4) will be detailed in the second paper [46].

The accuracy profile (Fig. 4) can simply be obtained by connecting the lower limits of tolerance or the upper limits of tolerance. As exemplified in Fig. 4, for the concentration levels C1 and C4, when the tolerance interval is larger than

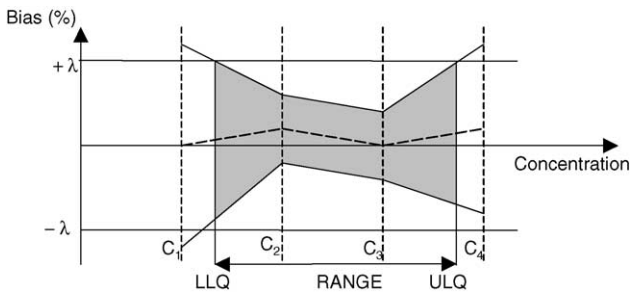

Fig. 4. Illustration of the accuracy profile as decision tool. LLQ, lower limit of quantitation; ULQ, upper limit of quantitation.

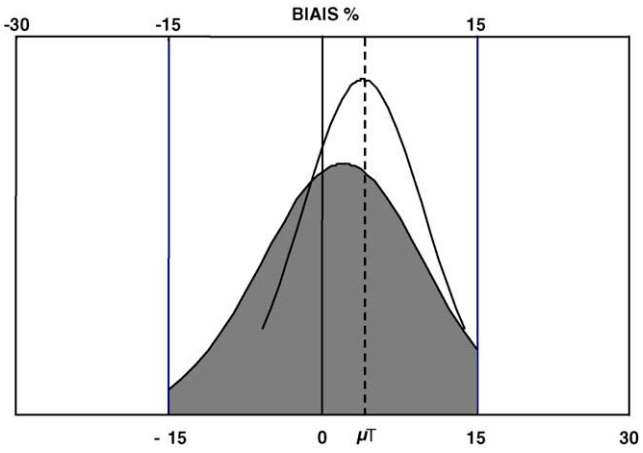

Fig. 5. Illustration of Eq. (4).

the acceptance limits, new limits of quantification and a new dosage interval have to be defined. Fig. 4 represents these new limits, namely the upper limits of quantitation (ULQ) and the lower limit of quantitation (LLQ). The latter is in perfect agreement with the definition of this criterion, i.e. the smallest quantity of the substance to analyze that can be measured with accuracy and a precision defined [1,5,6,10,11,40,44].

As can be seen from Fig. 4, the use of the accuracy profile as single decision tool allows not only to reconcile the objectives of the procedure with those of the validation but also to visually grasp the capacity of the analytical procedure to fit its purpose [40,44].

5. Conclusion

The lack of generalisation between the different validation protocols has conducted several analysts, resulting from different companies but also from previous SFSTP commissions on the validation (1992 and 1997) [20,21], to elaborate a harmonized approach. Moreover, if the first guides widely contributed to progress the analytical validations, they present, however, weaknesses regarding the conclusions of the tests carried out and thus the decisions to be made on the validity of the analytical procedures.

The present paper, which is the first part of the summary report of a new SFSTP commission on the validation of quantitative analytical procedures [1], mainly proposes to review the objectives of the validation according to the objectives of the analytical procedure and to distinguish the diagnosis rules and the decision rules. In this context, it is underlined that the objectives of validation are not simply to obtain estimates of bias and precision; it is to evaluate the risks or confidences that every single measurement that later will be performed in routine will be close enough to the unknown true value of the sample. In that respect, trueness, precision, linearity, and other validation criteria are no longer sufficient to make these guarantees. The adapted decision tool is the accuracy profile of the analytical procedure based on the β-expectation tolerance interval [52] and the concept of total error (bias + standard deviation). It allows not only to bring together the objectives of the procedure with those of the validation, but also to visually grasp the capacity of the procedure to fulfil its objectives and to control the risk associated with its use in routine [51]. The accuracy profile also permits to simplify the validation approach of an analytical procedure. The experimental design based on this concept as well as the consensus on the norms usually recognized for the validation of quantitative procedures will be presented and discussed in another paper [46]. The present approach applicable to various sector of analytical activity is a compromise, which appears to be reasonable and acceptable to all members of the commission with respect to the validation of a quantitative method.

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