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Harmonization of strategies for the validation of quantitative analytical procedures A SFSTP proposal – Part II

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Abstract

As reported in a previous paper [1], the main objective of the new commission of the Société Française des Sciences et Techniques Pharmaceutiques (SFSTP) was the harmonisation of approaches for the validation of quantitative analytical procedures. In a series of meetings, members of this Commission have first tried to review the objectives of analytical methods and the objectives of validation methods and to recommend the use of two-sided β-expectation tolerance intervals for total error of validation samples (accuracy profile) in the acceptance/rejection of analytical method in validation phase.

In the context of the harmonization, the other objectives were: (i) to propose a consensus on the norms usually recognized, while widely incorporating the ISO terminology; (ii) to recommend to validate the analytical procedure accordingly to the way it will be used in routine; (iii) to elaborate a rational, practical and statistically reliable strategy to assure the quality of the analytical results generated. This strategy has been formalised in a guide and the three latter objectives made by the Commission are summarised in the present paper which is the second part of summary report of the SFSTP commission.

The SFSTP guide has been produced to help analysts to validate their analytical methods. It is the result of a consensus between professionals having expertise in analytical and/or statistical fields. The suggestions presented in this paper should therefore help the analyst to design and perform the minimum number validation experiments needed to obtain all the required information to establish and demonstrate the reliability of its analytical procedure.

Keywords: Analytical procedure; Validation; Harmonization; Quantitative analysis; Accuracy profile; Total error; Experimental protocol

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1. Introduction

Irrespective of the sector of activity (chemistry, pharmacy, bio-pharmacy, food processing, environment, cosmetology, etc.), the goal of validation is to establish that the analytical method is suitable for its intended use, i.e. to prove the reliability of method results within well defined limits. An approach that is used currently is to define acceptance criteria based only on point estimates of assay parameters without an assessment of uncertainty. With this approach, the risk of accepting an unsuitable assay and rejecting a suitable assay are unknown and uncontrolled [2,3]. An alternative approach that controls these risks is to use accuracy profiles based on two-sided β-expectation tolerance intervals for total measurement error (including both bias and precision) of validation standards [4,5]. Such an approach reflects more directly the performance of individual assays and will result in fewer rejected in-study runs than the current procedure that compares point estimates of observed bias and precision with the target acceptance criteria, e.g. 2% (bulk drug), 5% (dosage form) or 15% (bioanalysis) [6]. It is why this approach has been adopted by the new SFSTP commission on the harmonisation of approaches for the validation of quantitative analytical procedures [1,7]. The accuracy profile constitutes for the analyst a visual tool allowing him to evaluate the capability of its method. In the context of harmonization, it is also needed to make the difference between the statistical tools that allow taking a decision (accuracy profiles) and the statistical tests that have a diagnostic purpose (estimation of trueness and precision). Indeed, as mentioned in the first part of the SFSTP guide [7], every analytical method is characterized by a "true bias" (systematic error) and a "true variance" (random error). These parameters are inherent in each method and they are also always unknown. In fact, an estimation of the method bias and variance can be obtained from the experiments carried out during method validation. These estimates will be more reliable if the experimental design and the number of experiments performed in the method validation are appropriate [8,9]. On the basis of these estimates for method bias and variance, the acceptance limits for the performance of the method make it possible to define the concept of "good analytical method" for a given field (e.g. bioanalysis) [4]. It is in this context that the statistical analysis of the validation results can find its real dimension and that the new commission proposed to review the bases of the analytical validation for developing harmonized approach, by distinguishing notably the diagnosis rules and the decision rules as reported in the first part of the SFSTP summary report [1,7].

On the other hand, considering official documents on validation of analytical methods [6,10–17], similarities (e.g. determination of accuracy, use of confidence intervals) and discrepancies (e.g. determination of linearity, interpretation of accuracy) can be found. It is why the new SFSTP guide also aims to propose in the present paper (part II of the summary report of SFSTP Commission [7]) a consensus on the norms usually recognized, while widely incorporating the ISO terminology. It also emphasizes the necessity to validate the analytical method in the same way it will be used in routine. However, as can be seen from the scientific literature, even if the validation criteria are defined, validation methodology together with practical experimental protocols are highly discussed [see for example 18–34] Thus, the new SFSTP guide finally presents an experimental strategy for the validation of the dosage 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. The overall SFSTP approach [1,7] will therefore minimize considerably the risk to accept a procedure that would not provide sufficiently accurate results or, to the opposite, to reject a procedure that would be capable [35,36].

Table 1
illustration of the interpretation of the concept of accuracy

	Accuracy vs. trueness
Statistics	Total error = systematic error + random error = bias + standard deviation
ISO [15,16]	Total error = trueness + precision = accuracy
ICH [10]	Total error = ? accuracy (Q2R1, Part I) [10] ? = accuracy (Q2R1, Part II) [10] + precision accuracy (Q2R1, Part II) [10] = trueness ISO [15]

2. Terminology

The following generally accepted validation criteria [6–17] are listed in the SFSTP guide:

Specificity – selectivity	Trueness
Response function (calibration curve)	Accuracy
Linearity	Limit of detection (LOD)
Precision (repeatability and intermediate precision)	Limit of quantitation (LOQ)
	Assay range

In addition, according to the domains concerned, other specific criteria can be required, for example the following ones: (i) analyte stability; (ii) recovery; (iii) effect of the dilution, etc.

It must be underlined that the validation criteria mentioned above must be evaluated, as much as possible, in the same matrix as the one of the samples intended to be analysed. Nevertheless, the definition of a matrix depends on analyst responsibility and some matrix regrouping, generally admitted by the profession for an application domain given, can be performed. Moreover, each modification of a previously validated method automatically involves a re-validation, the extent of which depends on the modifications made and their possible influence on specific validation criteria [7,12,37].

On the other hand, it is important to specify that there is not yet a global consensus between the various regulatory documents (ISO, ICH, AFNOR, SANCO, FDA, . . .) for the definition of the criteria to be tested during the validation step [6–17]. For example, the linearity criterion can appear or not and its interpretation can be different from one document to another [6,10–12,37–39]. It is the same for the trueness that can be confused with the accuracy according to the referential used [10–17] as illustrated in Table 1. The definitions of the validation criteria selected by the SFSTP Commission are most often those given in the ICH text Q2R1 [10] excepted for the four criteria, described below, for