FOR A GLOBAL APPROACH OF VALIDATION

Summary of the talk by Mr.FEINBERG (INRA Paris) at CECALAIT's AGM 2006

Within the context of the ISO 17025:2005 standard requirements, laboratories have to validate their alternative methods and estimate their uncertainties of measurement. To combine these two requirements, a global procedure, the exactitude profile method, constitutes a new approach. This procedure, composed of several stages described below, will constitute the body of the NF V 03-110 standard revision.

The life cycle of a method includes various stages:

- The selection, the conception and the development,
- The validation (intra and/or inter-laboratories),
- The uncertainty estimation,
- Routine use and performance control.

With the setting up of quality assurance systems in laboratories, the analysis method validation and the uncertainty estimation, required in the ISO 17025:2005 standard, are now important objectives. To verify if a method is adapted to its objectives, laboratories have to respond to the requirements described in the following articles:

- 5.4.5.1. Validation is the confirmation by examination and provision of objective evidence that the particular requirements for a specified intended use are fulfilled, and
- 5.4.5.2. The laboratory shall validate non-standardised methods, laboratory designed / developed methods, standardised methods used outside of their intended range and amplification or modification of standardised methods to confirm that the methods are fit for their intended use.

The validation strategy, which consists in verifying that the method gives a result that is different from the target, is inappropriate. Indeed, it leads to failures due to the fact that the less accurate methods are easier to validate.

The validation therefore orientates itself towards a different approach:

- The definition of an acceptability limit, representing the "intended use" of the method.
- The definition of the non-acceptable results probability:

  → To know the percentage of future non-acceptable measurements,

  → To define an interval, in which a known proportion of future measures will be, and to verify if it is within the acceptability zone.

The exactitude profile

The exactitude profile, constituting the body of the NF V 03-110 standard, permits to respond to these questions.

This new intra-laboratory validation approach is spread over several stages:

- The collection of calibration data,
- The collection of validation data,
- The prediction of concentrations found,
- The calculation of tolerance intervals,
- The building of the exactitude profile.

- **The collection of calibration data**

The objective of this stage is to establish the instrumental response function. The experimental plan contains measurements on samples at different levels and on several series of measurements (the series can represent the day, the operator or the instrument).

This stage is necessary only within the context of a method which does not directly give the concentrations of the analyte sought for.

- **The collection of validation data**

This stage is used to verify the performances of the method when using the applied operating procedure.

Several series of measurements on samples at different concentration levels are necessary to obtain the data required for this verification. The reference values assigned to different samples can be obtained in many ways: standard additions, reference method, reconstituted matrix or raw solutions, isotopic dilution…

- **The prediction of concentration**

The first stage consists in the building and the choice of calibration models using the calibration data. Various mathematical models can be used to calculate the method response function, but regression using the least squares method is the most accessible.

The second stage is the determination, by reverse prediction, of concentrations found in the validation samples (application of the reverse function to the response function determined during phase 1 of this stage).

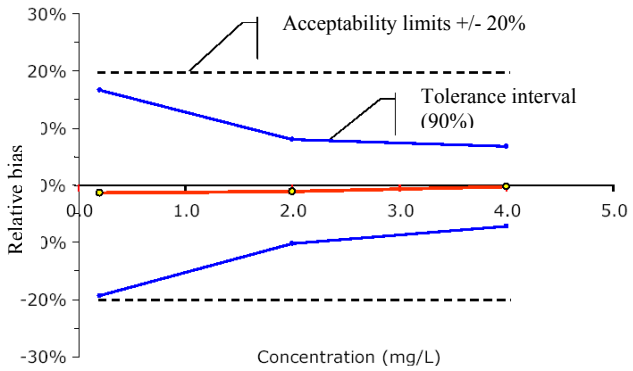
- **The calculation of tolerance intervals**

The statistical calculations are realised on concentration data found by reverse prediction. Then, the repeatability variance, the inter-series variance and the intermediary fidelity variance are calculated for each level, according to the principles described in the ISO 5725 standard.

Afterwards, a tolerance interval β can be deduced by level, in which a proportion β (generally 90%) of the future results of the method to be validated are expected to be found.

- **The building of the exactitude profile**

The exactitude profile is defined as a combination, represented in graphical form, of one or many tolerance intervals calculated at different levels and of an acceptability interval. It permits a global vision of the adequacy of the method's performances to the required specifications in the application field.



5- Exactitude profile (in % of the target)

The principle of the exactitude profile method is a global approach combining accuracy and reliability of the validated method. The decision concerning the validity of the tested method is realised directly on the graphical illustration. It also presents many other advantages such as:

- **The possibility of using numerous calibration models to calculate an instrumental response function,**
- **Its adaptation to large application fields, and**
- **The capacity to use a correction factor.**

However, the fixing of acceptability limits is a prerequisite to this method. With this approach, it is supposed that the data has a normal distribution, which constitutes an eventual disadvantage. But, in many situations, as for microbiological counts, this hypothesis is false. Nevertheless, a simple transformation of data into log permits to turn this limit around, as it has been demonstrated in several examples.