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NMR Interlaboratory Comparison Scheme

by

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1. INTRODUCTION

1.1 THE NEED FOR NMR INTERLABORATORY COMPARISONS

Since its first application as quantitative technique,[1] NMR spectroscopy has been successfully used for many applications involving several kind of matrix (small molecules, pharmaceuticals and natural products in both simple and complex mixtures).

One of the major advantages of quantitative NMR (qNMR) is its primary analytical characteristic. It can be applied in the quantitative estimation of purity of compounds without using any specific reference standard. Moreover, the recent progress in the development of high sensitive instruments allowed for reduction of the detection limits, thus making the technique appealing for analysis of molecules in very low concentrations. A comprehensive recent review aiming to extend awareness of experimental protocols for accurate NMR quantification of analytes is available in “Trends in Analytical Chemistry”.[2]

Despite the advantages deriving from the use of qNMR and despite the plethora of well documented validation processes (precision, accuracy, linearity, reproducibility, robustness, selectivity, and specificity), very few official NMR based quantification methods are known.

With the aim to extend the use of qNMR in official methods, Innovative Solutions organizes NMR interlaboratory comparisons (ILCs) according to ISO/IEC 17043:2010 and reference normative therein. ILCs provide objective standards for individual laboratories, permit them to compare analytical results from different laboratories and represent a way to check the quality and the accuracy of the analytical job. Validation by ILCs is the starting point for official recognition of the analytical methods.

The ILCs are organized by Innovative Solutions either for its own account or on behalf of third parties. In all cases, a scientific committee is responsible for the experimental design.

[1] J. L. Jungnickel, J. W. Forbes, Anal. Chem. 35 (1963) 938-942.

[2] S. K. Bharti, R. Roy, Trends in Analytical Chemistry, 35 (2012) 5-26.

1.2 REFERENCE NORMATIVE

- ISO/IEC 17043:2010 “Conformity assessment- General requirements for proficiency testing”.
- ISO/IEC 17025:2005 “General requirements for the competence of testing and calibration laboratories”
- ISO 5725:2004 “Accuracy of Measurement Methods and Results” - Parts 1-6
- ISO 13528:2005 “Statistical method for use in proficiency testing for inter-laboratory comparisons”.
- IUPAC TECHNICAL REPORT “ The international harmonized protocol for the proficiency testing of analytical chemistry laboratories”, Pure Appl. Chem., Vol. 78, No. 1, pp145-196, 2006.



2. THE SCHEME: Innovative Solutions NMR Inter-Laboratory Comparison (IS-NMR-ILC)

SCHEME FEATURES

The IS-NMR-ILC scheme is organized with the following steps:

- a) Call
- b) Registration
- c) Publication of the experimental instructions for participants
- d) Samples preparation
- e) Sample delivery
- f) NMR analysis
- g) Submission of the results
- h) Data elaboration
- i) Report publication

a. Call

The call makes known the aim of the ILC, the scientific committee, the customer for which Innovative Solutions (coordinator) organizes the ILC, the sample matrix and the NMR experiment selected for the ILC. Technical requirements of the participants are also indicated.

Concerning the costs, the customer can fund the ILC or can ask participants to pay a registration fee. When the customer funds the ILC, he becomes the owner of the data and decides on publication of the results.

b. Registration

Activation of the NMR Spectrometer Profile

In order to participate to IS-NMR-ILCs, a NMR Spectrometer Profile must be active on <http://nmr.mxcs.it/index.php>. Each participant will confidentially be provided with a unique identification username and password to login the NMR spectrometer profile. NMR spectrometer profile activation must be requested by email to ilc@innovative-solutions.it attaching (as pdf file) the registration form (see Annex 1) duly filled in and signed by legal representative.

If a participant plans to use more than one NMR spectrometer, additional NMR Spectrometer Profiles must be activated. Each participant must send one registration form per NMR spectrometer.

Activation of NMR Spectrometer Profile is free of charge and does not give any right to participate to interlaboratory comparisons.

Participation to the ILC

Participation to a specific ILC must be asked by email to ilc@innovative-solutions.it according to section 5 “Registration” of the “Call for participation”. Should a registration fee be due, bank transfer details demonstrating execution of the payment must be sent. After registration acceptance by Innovative Solutions, a link to the specific ILC will be active on the NMR Spectrometer Profile.



c. Publication of the guidelines for participants

General information and experimental instructions will be published on the NMR Spectrometer Profile. Instructions will be available only after registration is completed.

d. Samples preparation

Materials are carefully selected to meet the need of participants, and they are subjected to quality control. Details of test materials are given in the “Call for participation”. The test parameters are constantly reviewed to ensure they meet the needs of current laboratory testing and regulatory requirements. In order to check the quality of analytical materials, several factors such as homogeneity of the sample population, sample stability and all of the production steps are controlled. When possible, homogeneity tests are applied in accordance with IUPAC technical report “*The international harmonized protocol for the proficiency testing of analytical chemistry laboratories*”. Test material batches are tested for homogeneity for at least one test parameter where appropriate. Details of homogeneity tests and results are published on final report. In case of non-conformity, materials are retired. If this produces a delay, participants will be promptly apprised.

e. Samples delivery

Samples are sent by an express courier guaranteeing delivery within two days. Shipping codes will be given to participants in order to follow the way of packs. Samples are sent in an appropriate packaging, to guarantee the integrity of materials during transport. After delivery, the only responsible for preservation and disposal of the samples is the participant. Participants must verify the integrity of the received analytical material within 24 h from delivery. Any kind of problem must be quickly communicated to ilc@innovative-solutions.it (in case of broken materials, taking pictures is recommended). See paragraph 4.4 for appeals and complaints.

f. NMR analysis

Samples will be analyzed by participants, in accordance with methods and timetables provided by guidelines. Each deviation from instructions, if any, must be declared to coordinator before the submission of the NMR data.

g. Submission of the NMR data

Submission of the NMR data will be possible by on line procedure using the form on website <http://nmr.mxcs.it/index.php>. Participants can ask for a different result submission procedure. The possible different result submission procedure requires additional costs and must be communicated to Innovative Solutions no later than 15 days before deadline. After deadline, result submission is no longer possible.

h. Data elaboration

NMR data are submitted to a validated statistical elaboration procedure by Innovative Solutions staff, in accordance with the appropriate statistical principles of reference normative.



i. Report publication

Results of the statistical elaboration of the NMR will be published on the series titled “NMR Interlaboratory Comparisons” and will be available to the participants free of charge. Possible additional costs for non-participants will be decided by the customer.

Normally, report will be published within 45 working days after deadline.

E-book will be available depending on the decision of the customer (additional costs are required for hard-copy reports).



3.CRITERIA TO BE MET FOR PARTICIPANTS

Normally, no restrictions concerning hardware are applied unless NMR experiment selected for the specific ILC requires well defined hardware features.



4. INFORMATION FOR PARTICIPANTS

4.1 GUIDELINES FOR PARTICIPANTS

An instruction paper containing all information about ILC (NMR experiment, sample features, deadlines, costs, etc.) is drawn up for each program. All information are available on the NMR spectrometer profile. In case of changes of the ILC scheme design or operation, participants will be informed promptly by email.

Unless differently stated in the specific “Call for participation”, the minimum number of participants for each ILC is 10.

4.2 PRIVACY

Unless differently stated in the call, in the framework of an interlaboratory comparison, the identity of each participant will be unknown to other participants.

In order to guarantee the confidentiality of participants, a secret code will be assigned to each NMR spectrometer. In case of infringement of anonymity, the secret code can be changed under formal and written request.

4.3 SUBCONTRACT

In some circumstances, parts of the scheme may be executed by subcontractors. In such cases, Innovative Solutions will inform participants in advance. Even in case of subcontract, Innovative Solutions is responsible for all steps of the ILC.

Subcontracted steps, subcontractors and contact details will be declared in the “Call for participation”.

4.4 COMPLAINTS AND APPEALS

It is available a procedure for managing complaints to allow participants to appeal against valuation of their own performances. Records will be maintained of all complaints, appeals, investigations and corrective action taken.

For any kind of problem, contact Innovative Solutions by email to ilc@innovative-solutions.it.

4.5 COSTS

Possible costs (with payment details) will be declared in the “Call for participation”.

4.6 COLLUSION AND FALSIFICATION OF RESULTS

Innovative Solutions strongly stigmatizes collusion and falsification because they are contrary to professional scientific conduct. To participants falsifying results may be denied participation in successive comparisons. To prevent collusion and falsification, Innovative Solutions reserves the right to distribute more than one test material, so that participants cannot compare results.



5. CRITERIA FOR EVALUATION OF PARTICIPANT PERFORMANCE

Unless different evaluation will be appropriate, z-scores will be calculated for proficiency testing.

For z scores, the following limits must be considered:

- $|z| \leq 2.0$ indicates “satisfactory” performance;
- $2.0 < |z| < 3.0$ indicates “questionable” performance;
- $|z| \geq 3.0$ indicates “unsatisfactory” performance.

DETERMINATION OF THE ASSIGNED VALUE

Assigned values are determined in accordance with ISO 13528 by consensus value of results.

The ‘assigned value’ is the best estimation available for the ‘true’ value. The assigned value can be set as a consensus value. An estimate of the uncertainty of the consensus will be also provided. If the uncertainty is too high, z-scores may be issued for information only and should not be used by participants as fully evaluative of performance. The statistics for the derivation of the assigned value will be summarized in each ILC report. If necessary, reports will detail any complications in the derivations.