



NMR Interlaboratory Comparison Scheme

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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.

NMR spectroscopy can be considered an intrinsically quantitative analytical technique because of the direct proportionality between signal intensity and moles of the nuclei generating that signal. Quantitative NMR (qNMR) has become increasingly important for the analysis of pharmaceuticals, chemicals and natural products as well as for purity determination methods in pharmacopeia.^[2,3] Moreover, non-targeted analysis can be efficiently performed using NMR spectroscopy, which is able to provide significant information on the sample composition.^[4]

In recent years, an increasing number of studies were devoted to validation of the qNMR and non-targeted NMR methods. However, further efforts in protocol validation (including sample preparation, acquisition conditions, processing of the spectra and data analysis) are still needed to ensure accurate and reproducible results.

Inter-laboratory comparisons (ILCs) are the starting point for official recognition of the analytical methods. 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.

With the aim to validate the use of qNMR and non-targeted NMR methods, Innovative Solutions has already organized three ILCs, demonstrating the statistical equivalence of scaled NMR signals produced by different spectrometers and the possibility to create community-built analytical systems, including calibration systems.^[5,6,7,8]

The ILCs are organized by Innovative Solutions, according to ISO/IEC 17043:2010 and reference normative therein, either for its own account or on behalf of third parties. In all cases, a scientific committee is responsible for the experimental design.

[1] Anal. Chem. 35 (1963) 938-942 (<https://doi.org/10.1021/ac60201a005>)

[2] Magn Reson Chem. 59 (2021) 7-15 (<https://doi.org/10.1002/mrc.5099>)

[3] Magnetochemistry 7 (2021) 15 (<https://doi.org/10.3390/magnetochemistry7010015>)

[4] Food Analytical Methods 13(2020)530–541 (<https://doi.org/10.1007/s12161-019-01664-8>)

[5] Food Chemistry, 332 (2020) 127-339 (<https://doi.org/10.1016/j.foodchem.2020.127339>)

[6] Chemical and Pharmaceutical Bulletin, 68 (2020) 868-878 (<https://doi.org/10.1248/cpb.c20-00336>)

[7] Talanta, 214 (2020) 120-855 (<https://doi.org/10.1016/j.talanta.2020.120855>)

[8] Analytical Chemistry, 87 (2015) 6709-6717 (<https://doi.org/10.1021/acs.analchem.5b00919>)

1.2 REFERENCE NORMATIVE

- **ISO/IEC 17043:2010** “Conformity assessment - General requirements for proficiency testing”.
- **ISO/IEC 17025:2017** “General requirements for the competence of testing and calibration laboratories”
- **ISO 5725:2004** “Accuracy of Measurement Methods and Results” - Parts 1-6
- **ISO 13528:2015** “Statistical method for use in proficiency testing for inter-laboratory comparisons”.
- **IUPAC TECHINCAL REPORT** “The international harmonized protocol for the proficiency testing of analytical chemistry laboratories”, Pure Appl. Chem., Vol. 78, No. 1, pp 145-196, 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 aims of the ILC, the scientific committee, the customer, the funder, the coordinator, 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

Participation to a specific ILC must be asked using the form on <https://innovative-solutions.it/4th-nmr-interlaboratory-comparison/>

After registration acceptance by Innovative Solutions, a NMR Spectrometer User Page must be active on <http://nmr.mxcs.it>. If a participant plans to use more than one NMR spectrometer, additional NMR Spectrometer User Pages must be activated. Each participant must send one registration form per NMR spectrometer.



The participant will confidentially be provided with a unique identification username and password to login the NMR Spectrometer User Page.

c. Publication of the guidelines for participants

General information and experimental instructions will be published on the NMR Spectrometer User Page. 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 withdrawn. If this produces a delay, participants will be promptly apprised.

e. Samples delivery

Samples are sent by an express courier ensuring delivery within two days. Shipping codes will be given to participants to trace the way of packs. Samples are sent in an appropriate packaging, to ensure 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 amministrazione@samer.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 on the NMR Spectrometer User Page at <http://nmr.mxcs.it>

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.

Participant must follow instructions contained in the “Guidelines and contract terms” available in the NMR Spectrometer User Page. If instruction will not be complied, data will not be considered for final elaboration and the participant will not be considered in the final publication.

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.

Innovative Solutions will be the owner of the NMR data of the present ILC.

Raw NMR data will be not distributed to participants, neither entirely nor partly.

i. Report publication

Participants (only those who have complied with the instructions) will be mentioned in the final report and in any kind of publication containing NMR data they produced.

In case of publication in peer review journals, participants will co-author the manuscript according to the rule: 1 spectrometer, 1 co-author.



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.

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 available on the NMR Spectrometer User page. 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; maximum number of participants: 50.

4.2 PRIVACY

Unless differently stated in the call, in the framework of an interlaboratory comparison, the identity of each participant will be kept unknown to other participants till to the publication of the results. Moreover, the results and the performances will be shown in the final report by using a code which will be known only to the owner of the NMR spectrometer. In case of infringement of anonymity, the code can be changed under formal and written request.

4.3 SUBCONTRACT

The subcontract regulates:

- selection of NMR laboratories;
- sample preparation;
- shipping of samples to NMR laboratories;
- communication of the guidelines for running NMR experiments;
- organization and management of all activities and communications necessary for the collection of results.

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 question, contact SAMER (Contact Person: Katia Antonicelli) by email to amministrazione@samer.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 in qNMR.

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.

An appropriate multivariate statistical approach will be considered to assess performance in non-targeted NMR analysis.

DETERMINATION OF THE ASSIGNED VALUE IN qNMR

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.