

## LABORATORY STANDARDIZATION IN HEMATOLOGY

# External quality assessment scheme by private laboratories in Turkey

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### Abstract

At the end of this presentation the audiences should be able to understand the goal of external quality assessment and definitions used to describe similar functions of terminology. Also they had information about overview of interlaboratory method performance studies in Turkey in Hematology.

The past decade has been a time of significant change in international health. Reform in the United Nations system aims to make organizations more responsive to the needs of Member States, and to provide a rallying point for achievement of the International development goals. To rise to this challenge will require more emphasis on effectiveness through collective action and partnerships. This, in turn, will require more dynamic, and less bureaucratic, approaches to management assuming a greater role in establishing wider national and international consensus on health policy ([www.who.org](http://www.who.org));

- Strategies and standards through managing the generation and application of research, knowledge and expertise,
- Triggering more effective action to promote and improve health and to decrease inequities in health outcomes, through carefully negotiated partnerships and by making use of the catalytic action of others,
- Creating an organizational culture that encourages strategic thinking, prompt action, creative networking, innovation and accountability, and strengthens global influence.

The world is increasingly looking for greater coordination among development organizations. The global influence of the International Organization for Standardization (ISO) and the national health ministries from countries around the world, laboratories have come to embrace quality assurance as a system that combines daily quality control with interlaboratory

comparison and accreditation while looking at patient test results with any error in patient outcomes. In the quest for laboratory quality, proficiency testing, accreditation and the interlaboratory quality assessment programs are essential tools to measure progress.

For achieving this goal, non-profit organizations such as IFCC, ISH, NCCLS, ECCLS or national bodies; WHO, CAP, CMS, set effective performance characteristics for diagnostic tests to ensure reliable, traceable and comparable laboratory test results ([www.phppo.cdc.gov/CLIA/regs/toc.asp](http://www.phppo.cdc.gov/CLIA/regs/toc.asp)). Laboratory professionals take all necessary steps defined in quality assurance systems set by the above commitments. These concepts include:

- Test monitoring system
  - External QC (different from proficiency testing)
  - Internal monitoring
- Proficiency testing
- Analytical system quality assessment
- Calibration verification
- Quality assessment activities
- Personal competency assessment (ISLH XIVth International Symposium. Quality Assurance Workshop. External Quality Assurance Overview. RM Rowan.)

The programs under the establishment of quality management system in health services have been applied with the framework of the same concepts with different terminologies that is because the programs were named differently even their operating

Table I. Annual %CV values of CBC parameters of our programme and comparison with some others.

	Participant number	Hb	Hct	RBC	WBC	Trombocytes
2002	56	3.31	3.32	3.04	12.40	16.70
2003	53	2.83	3.94	3.45	14.81	14.22
2004	89	3.33	3.34	3.63	11.19	14.64
2005*	94	3.50	4.20	3.67	14.23	15.68
min-max		2.22–4.02	2.58–4.57	2.72–5.08	6.73–26.52	10.49–18.23
CLIA 88		7.00	6.00	6.00	15.00	25.00
ISLH		3.00	4.00	3.00	8.00	10.00
European Countries**						
min-max		1.70–3.20		1.90–3.00	3.60–8.90	6.50–17.00

\* First two distributions

\*\* JM Jou, Hematology external quality assessment in Europe, 2004 ISLH Congress

principles and concepts are not so much different. Since the terms defining the system have been used interchangeably so far, Codex Alimentarius Commission has suggested a new terminology to decrement the terminology to a unique structure (Appendix A).

Codex described proficiency testing as Inter Laboratory Exchange Programmes (ILEP) and described as a study in which several laboratories measure a quantity in one or more identical portions of stable materials under documented conditions. Major purpose of ILEP is to set method performance studies which include interlaboratory compatibility of results between different methods and instruments. ILEP will be used together with external QC material which gives a clue for evaluation of any new instrument or method. ILEP should include quality issues such as turnaround time, training and education of laboratory staff and appropriateness in test request and the utilization of the test results. Aim is to increase both efficiency and the operational effective-

ness. The data can be used for certification and accreditation. Organizational principles of ILEP are well established and clearly presented in guidelines released from IFCC, NCCLS/NCQA in case, could be adapted to hematology from ISLH.

Unfortunately there is no external quality assurance program neither in the area of Clinical Biochemistry nor in that of Hematology in Turkey. As Duzen Laboratories Group, our first study as starting point was peer view methods performance study to build up the compatibility among the test results between the private laboratories.

Turkish Hematology Society supports our interlaboratory peer view study because of:

- Determining the present situation in Turkey,
- Extending the content and improving to an EQAS programme from proficiency testing,
- Increasing the participation from hospitals to the programme.

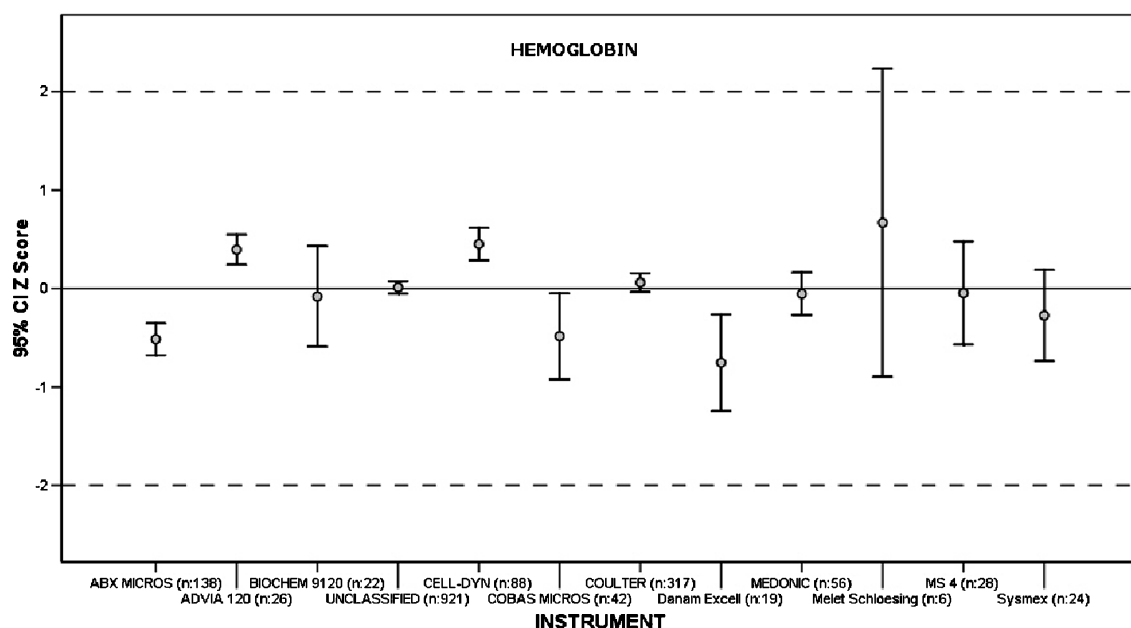


Figure 1. The distribution of variation described as SDI (z score) for Hb.

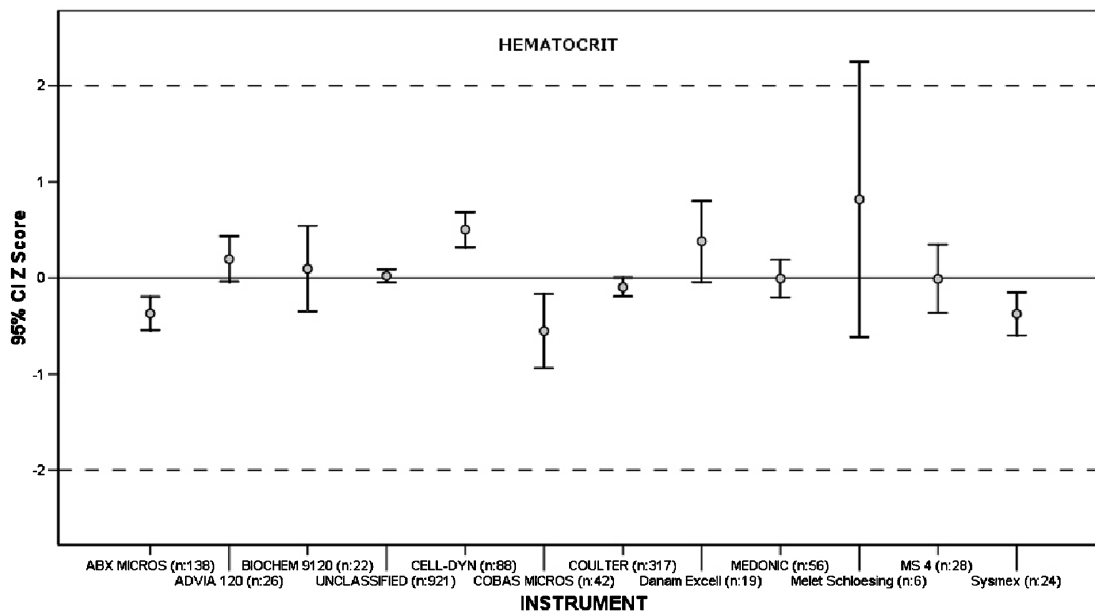


Figure 2. The distribution of variation described as SDI (z score) for Hct.

Furthermore within the last 2 years, TURKAK (Turkish Accreditation Agency) has undertaken the supervision of sample preparation, distribution and evaluation components of the program. The whole programme from sample preparation to evaluation is prepared and organized according to EQA programme given by IFCC (Fundamentals for External Quality Assessment, IFCC).

Participation to the programme is voluntary and the results are not linked to any sanctions. Results are submitted on code bases and keep confidential. Program was started with 54 laboratories and reached 110 as on June 2005 from all over Turkey. Fresh human blood is used which was taken from two

volunteer healthy donors, whose known infection risk is nons existent, and the programme includes measurement of Hb, Hct, RBC, WBC and thrombocyte counting. Homogeneity of the samples are controlled before distribution. Specimens are distributed 4 times in a year in temperature controlled conditions. Overnight delivery service is using for distribution and maximum time interval is 16 hours for arrival which makes possible to make the measurements in 14–18 hours. The participants send their results via Internet to our web site by using their username and passwords which are created by themselves. The anonymity of the results is provided carefully. The participants have 2 days for data entry and after 4 days they can see

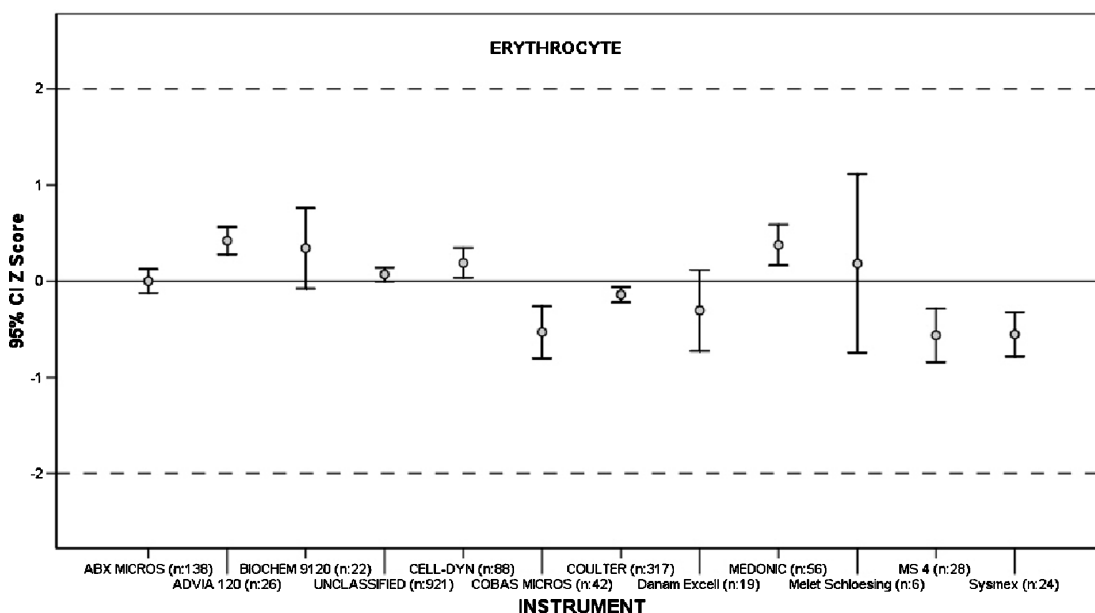


Figure 3. The distribution of variation described as SDI (z score) for RBC

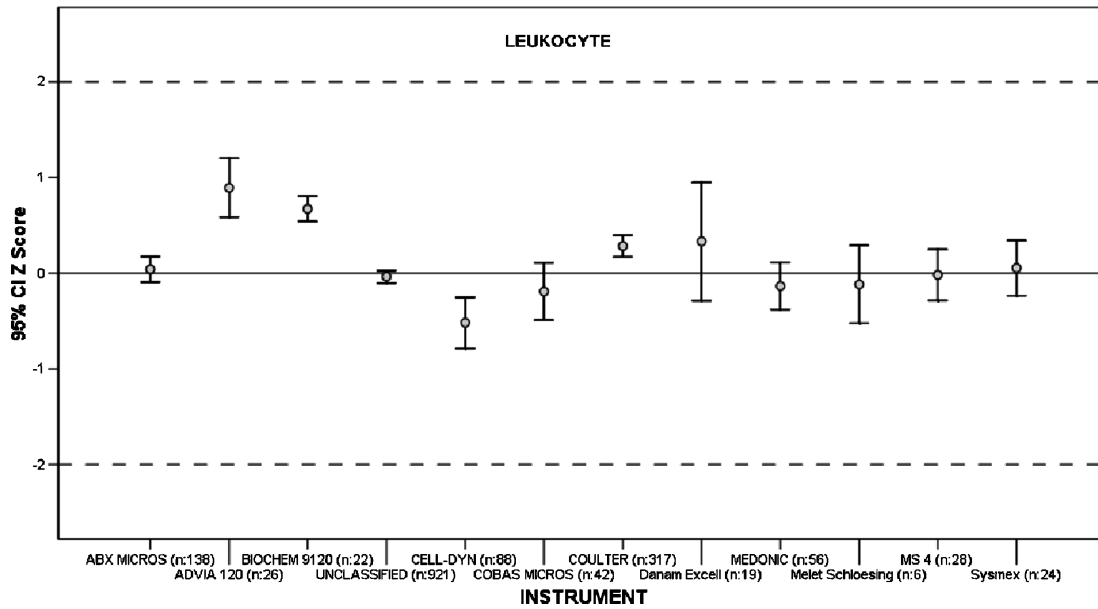


Figure 4. The distribution of variation described as SDI (z score) for WBC.

their whole reports and overall results of all participants to evaluate accumulated total results from the same web site ([www.duzen.com.tr/qcr](http://www.duzen.com.tr/qcr)).

An inhouse software programme that covers whole aspects of EQA programmes does the evaluation. Ranges of acceptability used in the programme have been set by IFCC and CLIA 88 criteria. Basic evaluation points in the programme are the consensus value and variation from the mean. All 4 last results in two different levels with mean, %CV, SD and SDI values are sent together with a Levey Jennings graphic

to the participants in printed reports. The participants can also see their results and special evaluations about the analyzers from Internet also. They can see their results in Youden graphics in which  $\pm 2SD$  and CLIA criteria are marked. Summary of accumulated overall results were submitted to TURKAK as well as the Turkish Hematology Society to be evaluated and discussed aiming to set a proper preparation, distribution and education system. Variations of the results for 4 years are given in Table I. Detailed report will be presented in oral presentation separately.

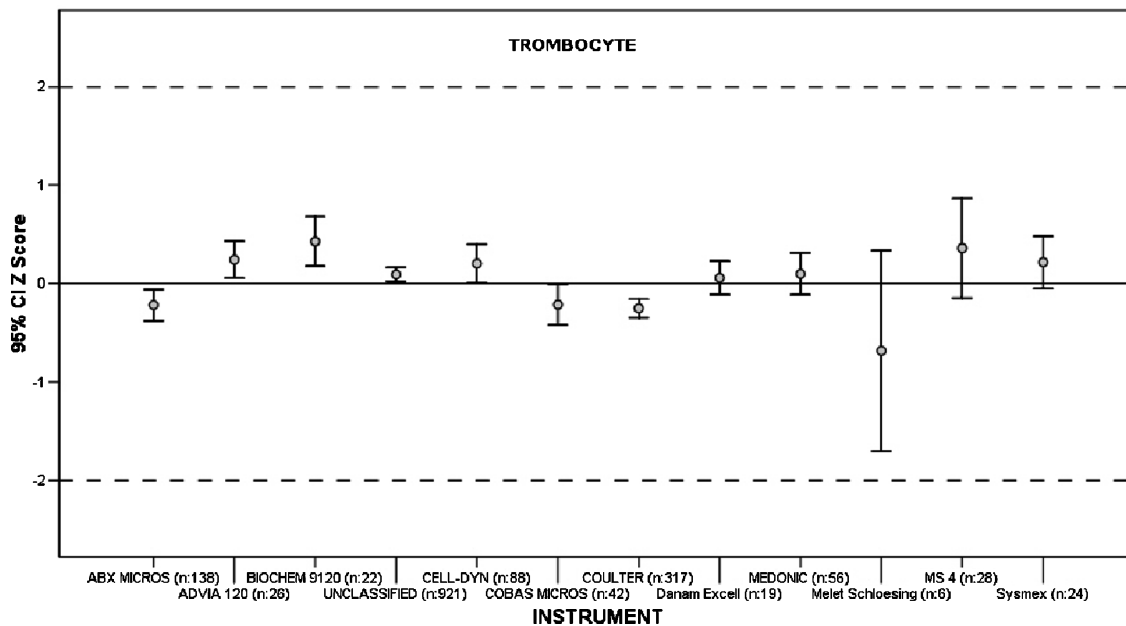


Figure 5. The distribution of variation described as SDI (z score) for trombocyte.

Table II. Within, between-subject variations and II value of CBC parameters (Biological variation: From principles to practice. CG Fraser, AACC 2005).

Analyte	Within-subject Variation (%)	Between-subject Variation (%)	Index of Individuality (II)
Hb	2.8	6.6	0.42
Hct	2.8	6.6	0.42
MCV	1.3	4.8	0.27
MCH	1.6	5.2	0.31
MCHC	1.7	2.8	0.61
RBC	3.2	6.1	0.52
WBC	10.4	27.8	0.37
Thrombocytes	9.1	21.9	0.42

Instrument based evaluation were made by using z scores (Figures 1–5). The z scores, which are in  $\pm 2$  value, are interpreted as the distribution shows acceptable variation. These findings seems like they are enough for the “first visit test” but in order to use these tests in monitoring, the CV values had to be better. Also the CV values had to decrease till to biological variations and the clinicians had to be instructed about the individuality index (II) (Table II). However CBC like tests with high II needs narrower variations to follow-up for monitoring or treatment to take a prompt action accordingly.

In order to add an extra value to our programme we make a special study in June 2005. The distributed sample is obtained from a single healthy donor and two levels of sample are prepared by taking and adding of plasma and buffy coat from one half to other. With this way we obtain 2 samples with different Hb, Hct, RBC, WBC and thrombocyte values and same RDW, MCH, MCV and MCHC

Table III. MCH, MCV, MCHC and RDW values that we obtain from our special study (Participant number =28).

	MCH		MCV		MCHC		RDW	
	Level 1	Level 2	Level 1	Level 2	Level 1	Level 2	Level 1	Level 2
	Mean	30.23	30.31	88.06	88.83	34.34	34.04	13.46
SD	0.86	0.85	2.13	2.29	1.03	1.02	1.04	1.11
CV%	2.85	2.80	2.42	2.58	3.00	2.99	7.75	7.95

values from the same person (Table III). In this study our aim was to see the variation between their results and the CV values that they obtain from their internal controls.

After presenting our preliminary findings in Hematology meeting at 2003, some of the kit providers started applying calibrators, therefore, routine calibrator users’s CV are presented. The calibrator using laboratories gives higher results as compared with others (Figure 6). We think that this is a relative result and the laboratories, which does not use calibrator gives false negative results. We will see the answer of this hypothesis with using reference material for our study in the near future.

So far we have achieved an agreement of over 95% with respect to CLIA. Since our goal is achieving further reduction in variation among the participating laboratories, to meet the ISH requirements rather than CLIA, will be the outcome on the aim of better gaining information about diagnostic accuracy (sensitivity) and limit of detection by reducing confidence limits of analyzer and calibrator. Rather than consensus value we would like to use control sample with a known value. Our aim is to use the samples that we

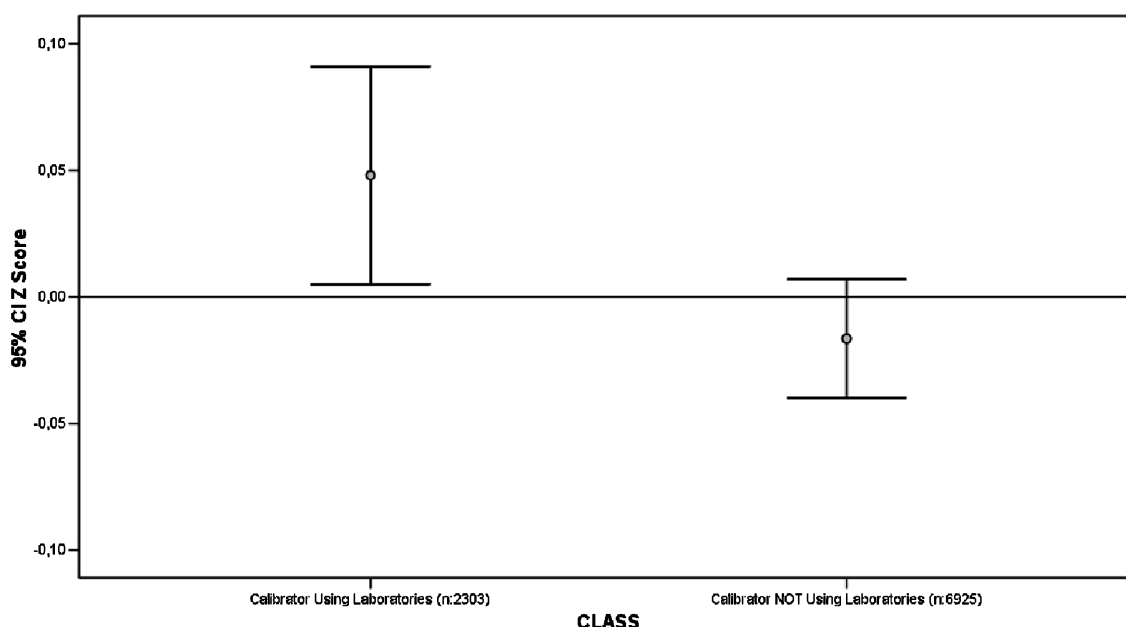


Figure 6. The distribution of variation described as SDI (z score) for calibrator using laboratories.

know their absolute values, which are prepared with reference methods. We believe this will change the discrepancies of calibrator user and reduce CV that this will be the correct way to reduce the CV values in order to use the consensus value. Our CV values do not change in years and there isn't any improvement. We know that we have to do something more but we think that this requires political enforcement of regulatory organizations and buyers of health services.

### **Acknowledgements**

I want to express my sincere appreciation to the programme supervisors for sharing the information about "Duzen Laboratuvarlar Arasi Kalite Kontrol Programi" and assistance for manuscript to Yalçin Yildiz.

### **Appendix A: Harmonisation of analytical terminology in accordance with international standards, inter-agency meeting may 2004**

#### **ACCURACY**

*ISO Standard 78-2: Chemistry – Layouts for Standards – Part 2: Methods of Chemical Analysis (Second Edition, 1999)*

Closeness of agreement between a test result and an accepted reference value.

NOTE: The term accuracy, when applied to a set of test results, involves a combination of random components and a common systematic error or bias component.

#### *As a concept:*

##### *Codex Alimentarius Commission*

The closeness of agreement between the reported result and the accepted reference value.

*Note:* The term accuracy, when applied to a set of test results, involves a combination of random components and a common systematic error or bias component. {ISO 3534-1} When the systematic error component must be arrived at by a process that includes random error, the random error component is increased by propagation of error considerations and is reduced by replication.

#### *As a statistic:*

##### *Codex Alimentarius Commission*

The closeness of agreement between a reported result and the accepted reference value. {ISO 3534-1}

*Note:* Accuracy as a statistic applies to the single reported final test result; accuracy as a concept applies to single, replicate, or averaged value.

##### *International vocabulary for basic and general terms in metrology*

##### *Harmonised guidelines for internal quality control in analytical chemistry laboratories*

##### *The international harmonised protocol for the proficiency testing of (chemical) analytical laboratories*

Closeness of the agreement between the result of a measurement and a true value of the measurand.

*Note 1.* Accuracy is a qualitative concept.

*Note 2.* The term precision should not be used for accuracy

#### **INTERLABORATORY STUDY**

##### *Codex Alimentarius Commission*

A study in which several laboratories measure a quantity in one or more "identical" portions of homogeneous, stable materials under documented conditions, the results of which are compiled into a single document.

*Note:* The larger the number of participating laboratories, the greater the confidence that can be placed in the resulting estimates of the statistical parameters. The IUPAC-1987 protocol (Pure & Appl. Chem., 66, 1903-1911(1994)) requires a minimum of eight laboratories for method-performance studies

**INTERLABORATORY TEST COMPARISONS*****International harmonised protocol for the proficiency testing of (chemical) analytical laboratories***

Organisation, performance and evaluation of tests on the same items or materials on identical portions of an effectively homogeneous material, by two or more different laboratories in accordance with pre-determined conditions.

**LABORATORY-PERFORMANCE (PROFICIENCY) STUDY*****Codex Alimentarius Commission***

An interlaboratory study that consists of one or more measurements by a group of laboratories on one or more homogeneous, stable, test samples by the method selected or used by each laboratory. The reported results are compared with those from other laboratories or with the known or assigned reference value, usually with the objective of improving laboratory performance.

***Notes***

1. Laboratory-performance studies can be used to support accreditation of laboratories or to audit performance. If a study is conducted by an organisation with some type of management control over the participating laboratories – organisational, accreditation, regulatory, or contractual – the method may be specified or the selection may be limited to a list of approval or equivalent methods. In such situations, a single test sample is insufficient to judge performance. It is expected that the results from 1 of every 20 tests will be outside the value for the calculated mean  $\pm$  twice the standard deviation, due solely to random fluctuations.
2. Sometimes a laboratory-performance study may be used to select a method of analysis that will be used in a method-performance study. If all laboratories, or a sufficiently large subgroup, of laboratories, use the same method, the study may also be interpreted as a method-performance study, provided that the samples cover the range of concentration of the analyte.
3. Separate laboratories of a single organisation with independent facilities, instruments, and calibration materials, are treated as different laboratories.

***Protocol for the design, conduct and interpretation of method-performance studies (1995)*****METHOD-PERFORMANCE STUDY*****Codex Alimentarius Commission***

An interlaboratory study in which all laboratories follow the same written protocol and use the same test method to measure a quantity in sets of identical test samples. The reported results are used to estimate the performance characteristics of the method. Usually these characteristics are within-laboratory and among-laboratories precision, and when necessary and possible, other pertinent characteristics such as systematic error, recovery, internal quality control parameters, sensitivity, limit of determination, and applicability.

***Notes***

1. The materials used in such a study of analytical quantities are usually representative of materials to be analysed in actual practice with respect to matrices, amount of test component (concentration), and interfering components and effects. Usually the analyst is not aware of the actual composition of the test samples but is aware of the matrix.
2. The number of laboratories, number of test samples, number of determinations, and other details of the study are specified in the study protocol. Part of the study protocol is the procedure which provides the written directions for performing the analysis.
3. The main distinguishing feature of this type of study is the necessity to follow the same written protocol and test method exactly.
4. Several methods may be compared using the same test materials. If all laboratories use the same set of directions for each method and if the statistical analysis is conducted separately for each method, the study is a set of method-performance studies. Such a study may also be designated as a method-comparison study.

***Protocol for the design, conduct and interpretation of method-performance studies (1995)***

An interlaboratory study in which all laboratories follow the same written protocol and use the same

test method to measure a quantity in sets of identical test items [test samples, materials]. The reported results are used to estimate the performance characteristics of the method. Usually these characteristics are within-laboratory and among-laboratories precision, and when necessary and possible, other pertinent characteristics such as systematic error, recovery, internal quality control parameters, sensitivity, limit of determination, and applicability.

## PRECISION

1. *ISO Standard 78-2: Chemistry – Layouts for Standards – Part 2: Methods of Chemical Analysis (Second Edition, 1999)*
2. *Codex Alimentarius Commission*

The closeness of agreement between independent test results obtained under stipulated conditions {ISO 3534-1}

Notes: {ISO 3534-1}

1. Precision depends only on the distribution of random errors and does not relate to the true value or to the specified value.
2. The measure of precision is usually expressed in terms of imprecision and computed as a standard deviation of the test results. Less precision is reflected by a larger standard deviation.
3. “Independent test results” means results obtained in a manner not influenced by any previous result on the same or similar test object. Quantitative measures of precision depend critically on the stipulated conditions. Repeatability and reproducibility conditions are particular sets of extreme conditions.

1. *Terms and definitions used in connections with reference materials, ISO Guide 30:1992*
2. *Harmonised guidelines for internal quality control in analytical chemistry laboratories*
3. *The international harmonised protocol for the proficiency testing of (chemical) analytical laboratories*

Closeness of agreement between independent test results obtained under prescribed conditions.

## NOTES:

1. Precision depends only on the distribution of random errors and does not relate to the accepted reference value.
2. The measure of precision is usually expressed in terms of imprecision and computed as a standard deviation of the test results. High imprecision is reflected by a larger standard deviation.
3. ‘Independent test results’ means results obtained in a manner not influenced by any previous result on the same or similar material.

## PROFICIENCY TESTING SCHEME

### *International harmonised protocol for the proficiency testing of (chemical) analytical laboratories*

Methods of checking laboratory testing performance by means of interlaboratory tests  
[It includes comparison of a laboratory’s results at intervals with those of other laboratories, with the main object being the establishment of trueness]

## QUALITY ASSURANCE

1. *Quality assurance and quality management-vocabulary, ISO 8402:1994*
2. *Harmonised guidelines for internal quality control in analytical chemistry laboratories*

All those planned and systematic actions necessary to provide adequate confidence that a product or service will satisfy given requirements for quality.