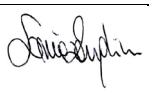
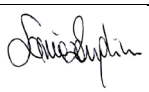
QUALITY SYSTEM qs@biogroupmedicalsystem.com

Date	Rev.	Reason	Drafting	Approval	Storage
03/29/2019	00	First issue	COP	RQS	RGQ
06/11/2019	01	Change in point 6.1 Exclusion from processing			
31/03/2020	02	Hematology PT insertion			
07/07/2020	03	Point variation 2-3-5			
05/26/2022	04	Corporate Change			
02/05/2023	**05**	**Changes following observations n°2 and 11 of the ispettivaACCREDIA visit on the 4th/08/2022**			

CLINICAL CHEMISTRY, IMMUNOLOGY and HEMATOLOGY EVALUATION TESTS monthly/quarterly

General information on organization and management

Manager **Legal and operative site**	Bio-Group Medical System Srl – Quality System Division Registered office: Via Latina, 20 – 00179 Rome Operational Headquarters: Loc . Campiano 9/B - 47867 Talamello (RN)-Italy TELEPHONE: +39 0541 920686 FAX: +39 0541 922130 E.MAIL: qs@biogroupmedicalsystem.com
Subcontracted activities	• Preparation of the proficiency test items QS Division uses highly qualified suppliers, certified and compliant with the standards set by standard 17043:2010 • Homogeneity and stability tests The data released by the supplier accredited/compliant with the UNI EN ISO/IEC 17025:2018 and UNI EN ISO/IEC 15189:2013 standards are viewed by the coordinator who evaluates their compliance. The homogeneity and stability data are available for consultation at the organization for a minimum period of four years.
Main reference document	UNI CEI EN ISO/IEC 17043:2010 Conformity assessment – General requirements for interlaboratory proficiency tests UNI EN ISO 9000:2015 Quality management systems – Fundamentals and vocabulary. ISO 13528:2015 Statistical methods for use in proficiency testing by interlaboratory comparisons JCGM 100 :2008 Evaluation of measurement data – Guide to the expression of uncertainty in improvement measurement results and methods , Part 1, 2, 3, 4, 5, 6. ILAC G13:08/2007 Guidelines for the Requirements for the Competence of Providers of ProficiencyTestingSchemes UNI CEI 70099:2008 International Metrology Vocabulary - Fundamental and general concepts and related terms (VIM)

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1. Introduction _

The final aim of the clinical analysis laboratory is to generate data on the patient's health status which will subsequently flow into the diagnostic process. For this reason it plays a primary role in defining the behavior that a clinician must follow to deal with a diagnosis or follow up of a therapy or condition.

The work carried out in a clinical analysis laboratory, therefore, must necessarily follow a series of procedures within a concept of quality to obtain a final data that respects the characteristics of precision and accuracy.

Each laboratory must be able to work in the best possible way while respecting quality rules so that the reports produced are as close to reality as possible. The data resulting from a clinical analysis may be affected by systematic and/or random errors. The more the operator knows the extent of these errors, the more he will be able to compensate the system by providing experimental data as close as possible to the real one.

The repeatability of the same analysis in the same working conditions (verified through the use of internal controls) is a first approach for the evaluation of errors . The comparison with a consensus average of multiple participants ensures and validates what was assessed with the internal controls .

Quality System represents an external quality assurance (EQA), i.e. it provides indications to consolidate the approach to laboratory quality control.

Quality System is the VEQ brand of Bio Group Medical System, Italian Proficiency Testing Provider.

The Proficiency Testing Providers are responsible for the organization of the interlaboratory proficiency tests (VEQ), from the design to the choice and preparation of the objects, to the homogeneity and stability checks of the materials, to the distribution of the samples to the participants, to the statistical analysis of the data up to the evaluation of the results and issuing of the report with the participants' performances.

The activity carried out by the Proficiency Testing Providers, therefore, is fundamental to allow the participating laboratories to monitor their performance over time, through participation on an ongoing basis.

interlaboratory proficiency tests in compliance with the UNI CEI EN ISO/IEC 17043:2010 standard demonstrates the technical competence of the organizer to design, organize and manage the tests indicated in the field of accreditation. The organizer of interlaboratory proficiency tests is in fact responsible for ensuring that the technical and management requirements, specified in the reference standard, are also satisfied by the collaborators and subcontractors involved in the test schemes subject to accreditation.

As regards the Accredia brand , it constitutes the formal demonstration of the competence, independence and impartiality of the organizer of the proficiency test by the national accreditation body. This brand also constitutes a tool and an opportunity to foster participants' trust in the service provided as a guarantee of its quality.

Bio Group Medical System is a PT Provider accredited ISO 17043:2010 by ACCREDIA (certificate n.17/P and related attachment downloadable from the website https://www.accredia.it/banks-dati/) .

2. Conditions for participation and registration in the PT

The following can join the QS: clinical analysis laboratories, multi-specialist diagnostic centres, nursing homes and similar bodies **.**

Expected number of participants: Given the QS Division's many years of experience in the sector, it is assumed that we can count on a number of 150 participants.

Registration is carried out directly by the laboratory concerned or through Distributors. In the case of direct participation by the laboratory or Italian Distributors , the manager of the center who

sends the request must have completed in all its parts and sent the registration form (MOD.18), the contract and the customer information Privacy.

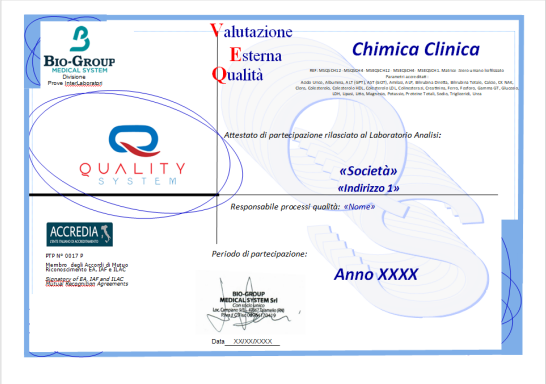
In the case of membership through a foreign distributor, the same will fill in the form. 27 summarizing the data from the analysis laboratories and the selection of the relevant evaluation tests.

The participant must ensure the availability of:

- Internet access
- PDF reading program
- Internet browsing browser

After having verified the conditions listed above, the QS division will proceed with the registration of the center by sending access credentials to the website (User and Password), the detailed instructions (ISTRU) for participation in the evaluation test and the calendar (mod. CAL) for and -mail or in paper form.

With the first submission of the OPV, the **certificate of participation** for the current year is issued.



The OPV package shipped contains the operating and usage instructions for the mod . IFU.
This INFO document can also be consulted on the Bio-Group MEDICAL SYSTEM Quality System division website.
In the event of changes in programming or in the case of the issue of revised Test Reports, participants are promptly informed via e-mail.

With each shipment, members of the system receive:

- *The samples to be analyzed*
- *IFU operating and use instructions*
- *Accompanying letter*

The participant can always contact the Quality Control Division of Bio-Group Medical System which is available for any clarifications or problems relating to the data processed by calling 0541920686 ext.3 or sending an email to qs@biogroupmedicalsystem.com

3. Test materials

The objects of the proficiency tests are materials simulating the biological finding usually analyzed by the participant for the test being tested . . These samples will present a range of values completely comparable with those found in the participants' work routine. To this end, those samples are chosen by the coordinator, which will give measurements referable to both physiological and pathological intervals.
The operating instructions and the relevant storage method are given in the IFU operating instruction.
The test methods are freely chosen by each participating laboratory.
In compliance with the recommendations of the UNI CEI EN ISO/IEC 17043:2010 standard (point 4.6.1.2), test samples must be treated with the same methods used for samples analyzed in everyday life. For each test parameter only one determination is normally required.

List of tests:

- Clinical Chemistry 1 monthly level 12 samples MSQSCH12-MSEQSCH12
- Clinical Chemistry 1 quarter level 4 samples MSQSCH4 - MSEQSCH4
- Clinical Chemistry 1 level 1 sample MS EQSCH1
- Immunology 1 monthly level 12 samples MSQSI12-MSEQSI12
- Immunology 1 quarterly level 4 samples MSQSI4 - MSEQSI4
- Immunology 1 level 1 sample MSEQSI1
- Hematology 8 parameters monthly 12 samples MSQSE812-MSEQUALITYE12
- Hematology 8 parameters quarterly 4 samples MSQUALITYE8-MSEQUALITYE8
- Hematology 8 parameters Annual 1 sample MSEQSE8

The parameters to test are the following:

Clinical Chemistry 1 level : Bile Acids*, Uric Acid, Albumin, ALT (GPT), AST (GOT), Amylase, ALP, Bicarbonates*, Direct Bilirubin, Total Bilirubin, Calcium, CK NAK, Chlorine, Cholesterol, HDL Cholesterol,

Cholesterol LDL, Cholinesterase, Creatinine, Iron, Phosphorus, Gamma GT, Glucose, LDH, Lipase, Lithium, Magnesium, Potassium, Total Protein, Copper*, Sodium, Triglycerides, UIBC*, Urea, Zinc*.
Test coordinator: Dr. Montini Matteo – QS Division of Biogroup Medical System Srl
* Parameters not covered by ACCREDIA accreditation

Immunology 1 level : 25 OH Vitamin D, ACTH*, Alpha FetoProtein , C Peptide*, CA 125, CA 15-3, CA 19-9, Carbamazepine*, CEA, Cortisol, DHEA Sulfate *, Digoxin*, Estradiol, Ferritin, Folate, FSH, FT3, FT4, β − HCG, HGH*, IgE, Insulin*, PTH*, LH, Phenobarbital *, Phenytoin *, Progesterone, Prolactin, PSA-FREE, PSA, T3, T4, Testosterone, TGAB*, Theophylline*, Thyroglobulin*, TMAB*, TPO AB*, TSH, Valproic Acid *, Vitamin B12*
Test coordinator: Dr. Montini Matteo – QS Division of Biogroup Medical System Srl

Hematology 8 Parameters: Erythrocytes (RBC), Leukocytes (WBC), Hemoglobin (HB), Hematocrit (HCT), Mean corpuscular volume (MCV) *, Mean corpuscular hemoglobin concentration (MCHC), Erythrocyte distribution width (RDW), corpuscular hemoglobin content Mean (MCH), Platelets (PLT), Mean Platelet Volume (MPV).
Test coordinator: Dr. Montini Matteo – QS Division of Biogroup Medical System Srl

*Parameters not covered by ACCREDIA accreditation

The evaluation test includes, depending on the frequency chosen, 1 / 4 / 12 determinations per year.
Each test material is subjected to checks by the QS Division in the COP function, guaranteeing the homogeneity and stability requirements according to the objectives required for the test itself. The tests are performed on a statistically significant number of aliquots according to the indications contained in the reference standard ISO 13528:2015.
In the event of a negative outcome of these checks, COP will inform RQS who will decide on the possible cancellation of the test by promptly notifying the participants of the test itself.
The test material is kept until the publication of the last test report of the relevant PT.

4. Purpose of the tests

The purpose of the QS is to allow a comparison between independent laboratories. The external quality assessment statistically examines the final result of the entire work process, therefore taking into consideration: the pre -analytical phase, the analytical phase and, finally, the post analytics which concerns the reporting and final transmission of the data.
From the results obtained with this control it is possible to make deductions on the good functioning of both the process itself as an organized structure and the various phases of which it is composed, arriving, in some cases, to obtain suggestions on the type of problem that leads away from a good result.

Participation in QS programs constitutes, in other words, a valid quality assurance tool for a laboratory.
The periodic control obtained through QS allows the operator to evaluate his own analytical system by comparing the results obtained with those of the daily CQI, thus validating it and the entire organization.
QS gives precise indications on any possible anomaly and therefore turns out to be a powerful tool for the constant improvement of "Total Quality" and data quality assurance.

5. Test execution timing

5.1 Dates and frequency of distribution

“Quality System” provides for the sending of samples to be analyzed according to the currently valid calendar mod. CAL (available on the QS website) . Subscriptions are accepted at any time of the year, OPVs will be sent from the current period to the end of the year. In the event that the shipping dates cannot be respected, participants will be informed by email.
The determinations and sending of the results via the web interface must be carried out as per the mod calendar. CAL.

5.2 Distribution methods

The OPVs are shipped by courier by the date set in the shipping calendar mod. CAL . The material is shipped to the headquarters of each registered laboratory directly or to distributors who guarantee shipment to the laboratories within the time limits and conditions as per the contract. Any inconveniences in receiving the material (delays beyond the expected 7 days, anomalies in the packaging or appearance, leakage of the material from the bottle, etc.) must be promptly reported to the QS Laboratory Testing Division. The availability of OPVs in addition to those distributed is guaranteed , limited to cases of non-delivery by the appointed carrier or accidental damage, in any case not beyond the time limits set for the execution of the determinations.

5.3Transmission of results

The results are transmitted, by the deadline established in the currently valid calendar (CAL form), through the reserved area of the qs-veq.it website, selecting the test in question; User and Password are always used for access.
To facilitate data entry operations, upon first access to the site's home page, the configuration of the Data entry tables is required where the participant will enter the tools and methods used for the tests. According to what is reported in paragraph 5.5.3 of the ISO 13528:2015 standard, the results must always be expressed in numerical form. Therefore, results of the type "<...", "below the detection limit" etc. are not permitted.

For each program there are different electronic reporting forms, for each of which the mandatory compilation of specific fields is required, without which it is impossible to proceed with the processing.

For each parameter you will be asked:

1) METHOD: the main analytical methods used by the laboratories are present
2) Unit of measure
3) INSTRUMENT
4) VALUE obtained from examining the samples.

All four of these data MUST be reported under penalty of exclusion from statistical processing, making inclusion in a consensus class difficult.

5.4 Issuance of Test Reports

The test reports will be published in the reserved area of the website on the date established in the currently valid calendar (CAL form), except for exceptions communicated in advance.

Participants who do not send the results within the established deadline will not be able to have an accredited test report.
Test reports will be available for four years from the date of publication.

6 Evaluation of laboratory performance and statistical data processing

In order to provide a tool that allows the participant an immediate and unambiguous assessment of the quality of the exam, the QS division in accordance with the ISO 13528:2015 standard carries out the statistical analysis as follows:

- The value assigned for each measurand is represented by the consensus average calculated according to the ISO 13528:2015 “A” algorithm, which allows the exclusion of aberrant values from the average, making this consensus average poorly influenced by erroneous values

- The measurement uncertainty of the assigned value is calculated on the standard deviation according to the formula: $U(X_{pt}) = 1{,}25\left(\frac{s}{\sqrt{p}}\right)$where:

  - s: robust standard deviation
  - p: number of participants

- Standard deviation σ: calculated according to the formula σ_{pt}= RSD% * $x_{pt}$where RDS% is the relative standard deviation calculated on the history of the parameter and $x_{pt}$is the consensus average of the parameter
- The evaluation of the laboratory's performance is expressed by the Z index calculated as follows: $Z = \frac{(x-X)}{\sigma}$where x is the consensus mean, X is the participant's measurement and σ is the standard deviation, and by the Z' index calculated as follows:

$$Z' = \frac{(x_i - x_{pt})}{\sqrt{\sigma_{pt}^2 + u^2(x_{pt})}}$$

Where $u^2(x_{pt})$represents the measurement uncertainty

- Since this is a performance evaluation on a consensus average, the Z-score and Z'-score indices are used alternatively:
  Z-score: it is calculated when the measurement uncertainty is negligible or $u(x_{pt})$< 0.3 σ_{pt}.
  Z'-score: it is calculated when the measurement uncertainty is non-negligible $u(x_{pt})$>0.3 σ_{pt}.

Typically the absolute value of Z obtained by the participant from indications summarized in the following diagram:

| Z |≤2 indicates "satisfactory" performance and does not generate any signal

2.0<| Z |<3.0 indicates "questionable" performance and generates a warning signal

| Z |≥3.0 indicates "unsatisfactory" performance and generates an intervention or Action signal

Shewart graphic representation is also provided which allows you to evaluate, for self-improvement purposes, the monitoring of performance over time.

6.1 Exclusion from Processing and Late Results.

The measurements entered affected by gross errors (e.g. typing error 2.1 instead of 21) will be excluded from processing; the participant will receive communication via email from the test Coordinator of the measure excluded and the detailed reason for the exclusion.

outlier measures are excluded using the Grubbs test. The participant will receive notification of the exclusion.

~~Statistical populations with fewer than 15 participants but more than 5 will be processed outside of accreditation and will receive an indicative performance index.~~

All statistical subpopulations whose number of participants is less than 5 are excluded from processing.

Also in this case, the Test Coordinator will inform the interested participants by email.

If the measurements are inserted after the last date for insertion, the wording "NA" (not applicable) will appear in the Z-score, D and D% fields. Also on the last page (summary) in these cases "NA" is shown on the last 4 columns of the table (Z/Z ', Z-score, D%, Remark). Also, late results will not be displayed in the shewart plot.

6.2 Reissue of test reports

The Coordinator can communicate the cancellation of a test report in the event of serious anomalies.
He will reissue the test report indicating its revision status.

7. Confidentiality

In the test report, QS will use the code assigned during registration for the test itself as the only identifying element of the origin of the data. The code is known only to the QS division and the laboratory in question. If the OPVs are sent to the distributor, the code is also known to the latter.

The participant must ensure that both the USER and the password assigned during registration are not disclosed to third parties; at the same time, QS division assumes the obligation of confidentiality in this regard.
The participant may agree to waive anonymity in order to:

- discuss your results;
- establish a process of mutual assistance to improve one's skills and performance;
- use the results for the purposes of external recognition (accreditation, etc.);
- communicate the results to competent authorities, who in turn may request that they be reported

results are provided officially by COP.

The test report, as it can only be downloaded from the reserved area of the dedicated website, is accessible to each individual participant and to the Quality System division . The test reports are available for 4 years from their issue.
The participant undertakes not to exchange information with others regarding the results of the determinations carried out as part of the Test.
In the presence of objective evidence of collusion between participants or falsification of results, QS reserves the right to exclude from the test the subjects who are responsible for such behaviors.

8. Reporting Complaints and Appeals

Participants in the tests who intended to submit Reports/Appeals/Complaints relating to aspects

connected with the conduct of the Tests, must submit a written request, accompanying it with the necessary documentation.

This request must be submitted to the email address qs@biogroupmedicalsystem.com and addressed to the test coordinator.