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ANALYST QUALIFICATION FOR COMPLIANCE WITH NORMAL ANALYTICAL PRACTICE FOR PIPETTE USE

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Aim. *This work aimed to assess the proficiency of routine medicine quality control analysts for compliance with the normal analytical practice (NAP) requirements for the standard pipette aliquoting analytical procedure.*
Materials and methods. *Certified 2 mL Mohr pipettes provided by the proficiency testing provider; a gravimetric procedure for determining the delivered volume and the corresponding equipment that meets the ISO 4787:2021 requirements; methods of mathematical statistics.*
Results and discussion. *The participants conducted five measurements of the delivered volume using the gravimetric method. The acceptance criteria for the results were developed to ensure reliable verification of volumetric glassware, where the random analyst's error had to be insignificant compared to the requirements for the error of the volumetric glassware, as well as compliance with NAP in routine analysis, particularly regarding individual deviations. A total of 64 analysts from 22 laboratories participated in the testing. Of these, 61 analysts achieved satisfactory results by all criteria. For 44 % of the participants, the deviations from the nominal value were significant as per the ISO requirements for Class A pipettes. Individual and average deviations from the nominal value were calculated and analyzed, allowing for assessing the participant results' precision and the correctness of their decisions regarding the ISO requirements for measuring equipment. The accuracy of the participants' calculations, the instruments used, and the testing conditions were evaluated. Issues with calculations, rounding of results, and non-compliance with the requirements concerning metrological balance qualification, thermometer calibration, laboratory environmental conditions, and pipette condition evaluation were revealed.*
Conclusions. *Findings indicate that participants can meet NAP requirements and perform pipette verification with high reliability, which aligns with the key analyst qualification requirements. The results confirm that for personnel qualification, it is necessary to use pipettes with certified delivered volume with acceptable uncertainty. The developed testing procedure can be used for intra-laboratory proficiency testing*
Keywords: *Mohr pipette, proficiency testing, measurement uncertainty, precision, State Pharmacopeia of Ukraine*

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1. Introduction

Participation in proficiency testing (PT) schemes provides laboratories with regular, objective, and independent assessments of the quality of routine analyses. In the pharmaceutical sector, participation in PT schemes is mandatory for official medicines control laboratories (OMCL) [1, 2]. Quality control laboratories of pharmaceutical manufacturers usually participate in PT schemes on their initiative. The Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines (USPCQM) is the PT provider for pharmaceutical quality control laboratories in Ukraine.

The most important application of PT schemes in the pharmaceutical sector is the external assessment of the quality of routine quantitative compliance testing. This type of testing involves making decisions about the compliance of a pharmaceutical product with specification limits [3]. The concept of measurement uncertainty is a modern metrological foundation used to ensure the reliability of decisions regarding compliance with specifications [4].

The key element of the uncertainty concept is the rule for making decisions on compliance with specifications. In the pharmaceutical sector, this rule has specifics defined by pharmacopeial standardization and is referred to as the pharmacopeial decision-making rule [5–7].

According to this rule, a laboratory can make a reliable decision on compliance with specifications provided the uncertainty of the reportable result does not exceed the value typical for normal analytical practice (NAP), i.e. the target uncertainty U^{tg} [8]. Typically, a necessary condition for this is that the uncertainty for typical individual analytical operations (such as weighing and dilutions in sample preparation, and measurements) also does not exceed the values typical for NAP $\left(U_i^{tg}\right)$. Recommended values for U_i^{tg} are provided in the Ph. Eur. Guide [9] and the State Pharmacopoeia of Ukraine (SPhU) [10].

Few publications are dedicated to PT schemes specifically for the pharmaceutical sector, and these often apply approaches from the non-pharmaceutical sector

without considering the specifics of the pharmaceutical one (e.g., [11]).

The key issue in assessing the quality of laboratory work for compliance testing is determining whether the laboratory can reliably decide on the compliance of pharmaceutical products in routine analysis. This can be achieved if the U^{tg} or U_i^{tg} values are used as criteria to evaluate the quality of results from PT participants. For over 20 years, the SPhU has actively embraced the concept of measurement uncertainty. Notably, it is only in the SPhU that recommendations regarding this uncertainty are explicitly published for main pharmaceutical tests (U^{tg}) and standard analytical operations (NAP requirements, U_i^{tg}) [10]. The compliance of laboratory participants in the PT scheme with the U^{tg} requirements for various pharmacopeial tests was assessed over 3–17 rounds of PT provided by the USPCQM.

It should be noted that the concept of uncertainty can be seen as part of the Analytical Quality by Design (AQbD) concept. The principles of AQbD aim to assure the quality of medicines by using enhanced approaches to designing, developing, and manufacturing medicinal products. The benefits of these integrated approaches include understanding, controlling, and mitigating sources of variation [12]. The impact of variation factors on the reportable result can be quantified using the uncertainty concept as a scientific basis [13].

The primary sources of measurement uncertainty in the pharmaceutical sector are often dilution operations and weighing [14, 15]. Therefore, controlling the uncertainty of sample preparation operations is a high priority for quality control laboratories of pharmaceutical products. For the correct functioning of the pharmacopeial decision-making rule, these standard operations must comply with the uncertainty requirements that any quality control laboratory of pharmaceutical products must meet (NAP requirements). Adhering to the NAP requirements ensures the acceptable reliability of procedure reproducibility described in the pharmacopeial monograph or Marketing Authorization Dossier [8, 14, 15].

Pipettes are more challenging to use than other types of volumetric glassware, such as burettes and volumetric flasks. During the investigation of factors influencing the quality of analytical results in pharmaceutical development, significant problems regarding the accuracy of aliquoting with a Mohr pipette were identified [16]. The investigation reviewed 97 aliquot-taking operations performed by four analysts in various experiments. The review found that 17 % to 83 % of the operations (depending on the experiment) did not comply with NAP requirements.

To our knowledge, studies on how laboratories meet the NAP requirements in routine analysis for individual standard operations, particularly volumetric ones, have not been conducted. The published analyst qualification procedures (e.g., [17]) focus solely on organizational aspects, such as intra-laboratory proficiency testing, without assessing the analyst's adherence to NAP requirements. Additionally, PT rounds dedicated to evaluating analysts' compliance with the NAP requirements for individual standard operations have not previously been carried out.

The results of our previous work dedicated to intra-laboratory staff training and testing [16] led us to the following conclusions:

1. To ensure proper personnel qualification for the aliquot-taking operation, it is necessary to use a pipette with a certified delivered volume with an uncertainty acceptable for the task. Verification of the pipette against ISO requirements alone is not sufficient.

2. Conducting a PT round for the entire pharmaceutical sector is relevant to find out how laboratories comply with the NAP requirements.

Therefore, USPCQM proposed the 18th PT round to assess laboratory compliance with the U_i^{tg} requirements. This assessment focused on the analyst's performance in the high-risk standard analytical operation of taking an aliquot with a 2 mL one-mark (Mohr) pipette.

This work aimed to assess the proficiency of analysts performing routine quality control of medicines for compliance with the NAP requirements for the standard analytical procedure of pipette aliquoting using the approach of the State Pharmacopoeia of Ukraine (SPhU).

2. Planning of the research

To achieve the aim of the work, it was necessary to solve the following tasks:

– prepare and carry out a PT round, including developing criteria for PT participants' results, establishing a test item (TI) calibration procedure, designing a test for PT participants, and running the round;

– analyze the PT participants' results for NAP compliance;

– assess the prospects of the proposed approach to confirming NAP compliance for the pharmaceutical sector.

The qualification criteria for analysts performing TI certification and the TI certification criteria were detailed in our previous publication [18]. However, as these aspects are integral to the implementation of the 18th PT round, they are briefly discussed in Section 4. Results (4. 1. Experiment design).

3. Materials and methods

3. 1. Materials and equipment

The materials included testing liquid, receiver vessel, balances, water thermometer, air thermometer, barometer, and time measurement devices. All materials adhered to the requirements of ISO 4787:2021. Mohr pipettes of ISO class A 2 mL provided by TECHNOSKLO, Czech Republic, were calibrated by the USPCQM using Mettler Toledo XSR 205 balances (Switzerland) and employed as TIs.

The SPhU metrological approach was used, and the results of the 18th PT round provided by the USPCQM were analyzed to assess the proficiency of analysts performing routine quality control of medicines.

3. 2. Analytical procedure for determining the delivered volume

1. Prior to the test, the pipette, all test equipment, and water shall have stood in the test room for a sufficient

time to reach equilibrium with the test room conditions. The temperature variation of the room during this time should not exceed 1 °C per hour. The equilibration time is usually about 2 hours, though it can be considerably longer.

Test water should be covered to avoid evaporation cooling.

2. The humidity of the air shall be recorded.

The test room shall have a relative humidity (RH) between 30 % and 80 %.

3. Atmospheric pressure shall be recorded.

4. Air temperature in the room shall be recorded.

The test room shall have a temperature between 17 °C and 25 °C with a maximum variation of ±1 °C during the test.

5. Water temperature shall be recorded.

The water temperature should be within ±0.5 °C of the air temperature.

6. Transfer an aliquot of the testing liquid using a 2 mL pipette into a pre-weighed receiver (if possible, use the tare function of the balance). To prevent water evaporation, cover the receiver and then weigh it. Based on the weighting results, determine the mass of the delivered water (m_{ij}).

7. Proceed as per steps 4–6, repeating the procedures five times.

8. Calculate the following based on the measurement results:

1) the delivered volume for each measurement (V_{ij});

2) the average result of the determination of the delivered volume $\left(\overline{V_i}\right)$;

3) the standard deviation (SD_i) of five repetitive measurements.

The calculated value of the found volume (V_{ij}) is determined under the requirements of ISO 4787:2021.

During testing, the analyst should handle the pipette according to ISO 4787, section 10 – Procedure for use.

3. 3. Statistical data processing

The results were processed according to the SPhU approaches [10, 19, 20].

4. Results

4. 1. Experiment design

Formulating general objectives for the PT round.

Further in the text, we refer to uncertainty as the expanded uncertainty for a 95 % confidence level when calculated from experimental data. This expanded uncertainty corresponds to a one-sided confidence interval of 95 %.

To determine the delivered volume, the gravimetric method for calibrating volumetric glassware, as described in ISO 4787 [21], was proposed.

The general objectives for the round can be defined based on the key requirements for personnel qualification for routine quality control of pharmaceutical products as follows:

1. An analyst must be capable of verifying volumetric glassware for compliance with ISO class A requirements [22].

According to ISO requirements, the maximum allowable deviation from the nominal volume $\left(U_{ISO}^{tg}\right)$ for 2 mL class A pipettes is 0.010 mL or 0.50 %. Typically, the nominal volume is compared to the average volume measurement $\left(\overline{V}\right)$ from 3–5 replicate determinations.

To ensure the reliability of verification results, when performing a series of n successive measurements of the delivered volume (V_i), an analyst has to achieve the uncertainty for $\overline{V}$ (precision component – Δ_v) that is insignificant compared to U_{ISO}^{tg} [10, 20]:

$$\Delta v \le 0.32 \times U_{ISO}^{tg}, \%;\ \Delta v = RSD_{V_i} \times t / \sqrt{n}, \qquad (1)$$

where t is the one-sided 95 % Student's t-coefficient for a number of degrees of freedom $\nu = n-1$.

We have demonstrated that the insignificance for precision is achieved with high reliability for 2 mL Mohr pipettes after 5 volume measurements (n=5) [23].

2. In routine analysis, an analyst has to be capable of taking an aliquot (V_i) with a deviation from the nominal value that does not exceed the requirements of the NAP.

This requirement must be met for any aliquot taken in routine analysis with high reliability. The NAP requirements for the 2 mL Mohr pipette were justified at a 0.012 mL (0.61 %) level [23].

It should be noted that the NAP requirement exceeds the maximum permissible deviation from the nominal volume under the ISO Class A requirements for volumetric glassware. The NAP requirement accounts for the additional random variation introduced by the analyst in routine analysis. This increase in the influence of precision on the total uncertainty for the aliquot volume occurs because the analyst takes an aliquot only once to prepare the test or reference solution in routine analysis. During verification, the aliquot is taken several times, and the contribution from precision decreases due to the averaging of results.

The above-mentioned qualification requirements define the criteria for PT participant's results and the characterization of TIs (pipettes).

Previous steps for the 18th PT round.

Planning the PT round.

Test task No. 1 of the 18th round of PT was dedicated to assessing the work of an analyst in performing standard operations – specifically, taking an aliquot with a Mohr pipette of ISO class A with a nominal delivered volume of 2 mL. The PT provider certified the pipettes, making the nominal volume the certified value. Participants of the round (laboratories) were encouraged to involve several analysts who routinely participate in quality control analyses of pharmaceutical products. The testing was carried out with the following objectives:

– to ensure the correctness of the procedure for handling Mohr pipettes;

– to provide participants with the necessary information to identify problems and improve their work with pipettes;

– to offer participants recommendations regarding the criteria for assessing the analyst's qualification when working with Mohr pipettes.

According to the purpose of testing, the following tasks were set for PT participants:

1. Conduct five replicate determinations of the delivered volume using the test pipette according to the provided methodology.

2. Submit the results of the volume determinations by filling out a protocol form.

Test item certification.

An approach to TI certification by the PT provider was formulated based on the key requirements for personnel qualification:

– the characterization of each TI was conducted by three analysts to ensure reliability;

– these analysts were trained and tested using pipettes with a certified delivered volume provided by the pipette producer;

– to ensure acceptable uncertainty for the characterization of TIs (certified volume value assigned to the *i*-th pipette – V_i^{Cert}), the procedure for determining the delivered volume was optimized by fixing the pipette in a stand and reading the meniscus position using a magnifying glass.

Confirmation of qualification of analysts involved in TI certification.

The purpose of testing the analysts was to confirm their capability to ensure that the uncertainty for V_i^{Cert} was insignificant in comparison with the key requirements for personnel qualification. All proposed acceptance criteria were achieved [18].

TI characterization.

2 mL class AS Mohr pipettes, which are identical to ISO Class A in acceptance criteria, were purchased.

All three analysts calibrated each pipette by performing five weighings of the delivered volume. Acceptance criteria for the characterization results of TIs were proposed to confirm the insignificance of V_i^{Cert} with respect to the key requirements for personnel qualification. All proposed acceptance criteria were achieved [18].

To avoid unforeseen errors in determining V_i^{Cert}, only those pipettes for which V_i^{Cert} insignificantly deviated from the nominal content were used as TIs, i.e. the following inequality was satisfied:

$$\left|V_i^{Cert} - 2.000\right| \le 0.32 \times 0.5\ \% = 0.16\ \%. \qquad (2)$$

Current steps for the 18th PT round.

Planning the test task for PT participants.

One TI was planned to be sent to each participant (laboratory). Each analyst from a participating laboratory should perform five delivered volume measurements. Analysts should calculate:

1) the delivered volume for each measurement – V_{ij};

2) the average result of the determination of the delivered volume $\left(\overline{V_i}\right)$;

3) the standard deviation (SD_i) of five repetitive measurements.

A Protocol containing a Good Laboratory Practice Compliance (GLP) Questionnaire was developed for PT participants. This Questionnaire aimed to analyze how well participants adhere to GLP recommendations, which is necessary for obtaining reliable analysis results.

Criteria for evaluating the results of participants in the PT round.

The criteria for evaluating the participants' results must be developed based on the key requirements for personnel qualification and the experience gained during the PT round preparation.

Planning for results processing.

The participants' experimental results need to be evaluated for compliance with criteria developed based on the key requirements for personnel qualification. Additionally, it is necessary to check the correctness of calculations and the presentation of results (rounding) as errors by participants were noted in previous rounds (see, for example, [24]). The responses in the Questionnaire also need to be analyzed to ensure compliance with the execution of the experiment according to GLP recommendations.

4. 2. Development of criteria for evaluating the results of PT participants

Criteria regarding the measurement of the delivered volume.

Based on the key requirements for personnel qualification and considering the experience gained parameters for evaluating the results of PT participants criteria for the proposed parameters were suggested in the test task.

Parameter A: bias. Deviation of the average result of the determined delivered volume $\left(\overline{V_i}\right)$ from the nominal value of 2 mL.

Criterion *a*:

$$\overline{d_i} = \left|\overline{V_i} - 2.000\right| \le U_{ISO}^{tg};\ \ \overline{d_i} \le 0.010\ \text{mL}. \qquad (5)$$

This parameter is used because the analyst performing routine analyses should be able to verify the volumetric glassware correctly. For the verification of volumetric glassware, the analyst must reliably determine the deviation of the experimentally determined mean volume for a unit of the glassware being tested from the nominal volume value.

The deviation of the average result when determining the delivered volume from the reference value allows for the systematic error in the analyst's work to be assessed. Following the SPhU concept, the systematic error for the operation of taking an aliquot should be insignificant compared to the maximum allowable uncertainty of the pipette according to NAP requirements (not more than 0.012 mL×0.32=0.0038 mL or 0.61 %×0.32=0.20 %). However, the organizers found that such a criterion is unachievable for routine analysis. Therefore, a criterion based on the key requirements for personnel qualification was applied.

Parameter B: *NAP compliance for individual deviations.* Individual deviations of the delivered volume from a nominal value of 2 mL $\left(V_{ij}\right)$.

Criterion *b*: for any V_{ij} :

$$d_{ij} = \left|V_{ij} - 2.000\right| \le U_{NAP}^{tg}, \quad (6)$$

where U_{NAP}^{tg} is the maximum permissible uncertainty for working with a pipette, as per the SPhU recommendations for NAP requirements (0.012 mL or 0.61 %).

The parameter and criterion are key requirements for personnel qualification. They ensure comparability of routine analysis results among different analysts, over time, and between different laboratories.

Parameter C: precision. Standard deviation (SD_i) of five repetitive determinations of delivered volume.

Criterion *c*:

$$SD_i \le 0.0034 \text{ mL}. \quad (7)$$

This criterion ensures that the precision component of the variation in results is insignificant compared to the ISO requirements for the verification of 2 mL class A pipettes using five repetitive measurements (as recommended by the SPhU [19]). This translates to a 95 % reliability of verification results for volumetric glassware [23].

Parameter D: correctness of decision on ISO compliance for volumetric glassware. Analysts had to evaluate the pipette's compliance with ISO Class A requirements (ISO 648, [22]) based on the obtained results.

Criterion *d*:

– correct decision on compliance with ISO:

$$\left|V_i - 2.000\right| \le U_{ISO}^{tg};$$

– correct decision on non-compliance with ISO:

$$\left|V_i - 2.000\right| > U_{ISO}^{tg}.$$

One key requirement for personnel qualification is that the analyst be competent in verifying glassware and making a reliable decision about compliance with the ISO standard.

Decision regarding the compliance of analyst`s results. Results that meet the four specified above criteria *a-d* are considered satisfactory.

Assessing compliance with Good Laboratory Practice (questionnaire).

Additionally, participants' adherence to testing procedure requirements was evaluated, which is an indicator of the laboratory's ability to properly conduct the qualification of volumetric glassware and meet the requirements of generally accepted laboratory practices according to the following parameters:

– the presence of metrological verification and qualification of balances;

– compliance of thermometer parameters with the requirements of ISO 4787:2021;

– compliance of laboratory environment conditions with the requirements of ISO 4787:2021;

– presence of procedures for evaluating the condition of the pipette as per ISO 4787:2021.

Verification of the correctness of calculations performed by analysts.

The provider recalculated the results provided by participants based on the primary results to detect errors. The provider also assessed the correctness of the presentation of results (rounding).

4. 3. Discussion of results obtained from PT round participants

64 analysts from 22 laboratories participated in the 18th PT round, including:

– 18 laboratories of pharmaceutical companies in Ukraine;

– 1 laboratory of the territorial bodies of the State Service of Ukraine on Medicines and Drugs Control;

– 3 laboratories of other organizations in Ukraine authorized for official quality control of medicines.

From 1 to 6 analysts from the participating laboratories (as determined by the laboratory) took part. The goal was to provide an opportunity to assess the capabilities of the entire laboratory to conduct routine analysis correctly.

4. 3. 1. Evaluation of results according to acceptance criteria for parameters *a–d*

The acceptability of the participant's results was evaluated based on criteria *a-d*, specified in section 4. 2. Table 1 presents the participants' results and the assessment of their acceptability.

Table 1

Results of delivered volume measurements with pipettes by the 18th round's participants

Laboratory No.	Analyst No.	$\overline{d_i^*}$ (≤0.010 mL)	max $\overline{d_{ij}^{\#}}$ (≤0.012 mL)	$\overline{SD_i^{\dagger}}$, mL (≤0.0034)	Decision on ISO compliance‡	Decision regarding the adequacy of the analyst's results§
1	2	3	4	5	6	7
1	1	–0.006	–0.007	0.0002	correct	complies
2	1	0.010	0.012	0.0018	correct	complies
3	1	–0.007	–0.008	0.0010	correct	complies
4	1	–0.001	0.007	0.0032	correct	complies
	2	0.001	0.004	0.0029	correct	complies
	3	–0.066	–0.076	0.0083	correct	does not comply
	4	–0.006	–0.007	0.0010	correct	complies
	5	–0.009	–0.009	0.0003	correct	complies

Continuation of Table 1

1	2	3	4	5	6	7
5	1	–0.002	–0.006	0.0032	correct	complies
	2	0.009	0.010	0.0012	correct	complies
	3	–0.004	–0.006	0.0015	correct	complies
	4	–0.001	–0.004	0.0028	correct	complies
	5	0.000	0.003	0.0027	correct	complies
6	1	0.003	0.003	0.0003	correct	complies
	2	0.002	0.003	0.0008	correct	complies
	3	0.002	0.003	0.0003	correct	complies
	4	0.002	0.003	0.0005	correct	complies
	5	0.006	0.008	0.0011	correct	complies
7	1	–0.006	–0.008	0.0020	correct	complies
8	1	–0.009	–0.012	0.0027	correct	complies
	2	–0.002	–0.004	0.0022	correct	complies
	3	–0.008	–0.009	0.0020	correct	complies
9	1	–0.021	–0.023	0.0015	incorrect	does not comply
10	1	0.001	0.002	0.0009	correct	complies
	2	0.001	0.002	0.0007	correct	complies
	3	–0.001	–0.002	0.0006	correct	complies
11	1	0.000	–0.003	0.0020	correct	complies
	2	–0.007	–0.010	0.0028	correct	complies
	3	0.009	0.014	0.0033	correct	does not comply
12	1	0.002	0.006	0.0028	correct	complies
	2	0.007	0.008	0.0004	correct	complies
	3	0.008	0.009	0.0010	correct	complies
13	1	–0.004	–0.004	0.0006	correct	complies
14	1	0.000	±0.001	0.0010	correct	complies
15	1	0.001	0.003	0.0016	correct	complies
	2	0.002	0.005	0.0029	correct	complies
	3	0.001	0.005	0.0023	correct	complies
	4	0.000	0.002	0.0015	correct	complies
16	1	–0.007	–0.009	0.0013	correct	complies
	2	–0.009	–0.010	0.0008	correct	complies
	3	–0.007	–0.009	0.0016	correct	complies
	4	–0.007	–0.008	0.0011	correct	complies
	5	–0.005	–0.006	0.0013	correct	complies
17	1	0.002	0.004	0.0014	correct	complies
	2	0.002	0.006	0.0025	correct	complies
	3	0.004	0.006	0.0012	correct	complies
	4	0.002	0.004	0.0015	correct	complies
	5	0.003	0.003	0.0013	correct	complies
	6	0.002	0.003	0.0008	correct	complies
18	1	–0.004	–0.004	0.0002	correct	complies
19	1	–0.001	0.002	0.0011	correct	complies
	2	0.001	0.004	0.0027	correct	complies
	3	0.000	–0.004	0.0024	correct	complies
	4	–0.002	–0.003	0.0008	correct	complies
	5	0.000	0.003	0.0021	correct	complies
	6	–0.001	–0.002	0.0013	correct	complies
20	1	–0.006	–0.007	0.0012	correct	complies
	2	–0.007	–0.009	0.0019	correct	complies
	3	–0.006	–0.010	0.0025	correct	complies

Continuation of Table 1

1	2	3	4	5	6	7
21	1	–0.002	–0.003	0.0013	correct	complies
	2	–0.001	–0.002	0.0009	correct	complies
	3	–0.004	–0.007	0.0029	correct	complies
22	1	0.003	0.004	0.0011	correct	complies
	2	0.001	0.002	0.0003	correct	complies

*Note: * – deviation of the average volume from the nominal value, mL; # – maximum deviation of a single volume from the nominal value, mL; † – standard deviation of five repeated determinations, mL; ‡ – participant's conclusion on the pipette's compliance with ISO requirements; § – assessment of the test result by the PT provider. Text for results not meeting the acceptability criteria is highlighted in grey.*

Out of 64 analysts, satisfactory test results according to criteria *a*-*d* were obtained by all participants, except for the following:

– laboratory 4 (5 analysts participated), analyst No. 3: criteria *a*–*c* were not met;

– laboratory 9 (1 analyst participated): criteria *a*, *b*, *d* were not met (conclusion about the pipette's compliance with ISO requirements not provided);

– laboratory 11 (3 analysts participated), analyst No. 3: criterion *b* was not met.

Below is the total number of non-complying results according to the acceptance criteria *a*–*d*:

The total number of non-complying results according to the acceptance criteria *a*-*d* is as follows:

– criterion *a* (bias): 2;

– criterion *b* (NAP): 3;

– criterion *c* (precision): 1;

– criterion *d* (decision): 3.

Table 2 presents the individual results of determining the volume delivered by the pipette for analysts who had non-compliance according to criterion *b*.

Table 2

Individual results of delivered volume measurements with pipettes by analysts not meeting criterion *b*

Laboratory No	4	9	11
Deviations from the certified value of d_{ij} (NAP criterion≤0.012mL)	–0.063 mL	–0.021 mL	0.007 mL
	–0.076 mL	–0.023 mL	0.007 mL
	–0.071 mL	–0.021 mL	0.014 mL
	–0.065 mL	–0.020 mL	0.007 mL
	–0.054 mL	–0.019 mL	0.012 mL

Note: results not meeting criterion b are highlighted in grey.

5. Discussion

Assessing the risks associated with variation and its impact on the accuracy of decision-making regarding compliance with specifications is a critical priority for laboratories conducting compliance testing.

However, existing publications on PT schemes in the pharmaceutical sector predominantly focus on comparative results between laboratories. They do not address the specificities of pharmaceutical standardization – particularly pharmacopoeial decision-making rules and the pharmacopoeial approach to constructing content limits. Overlooking these specificities can result in skewed risk assessments. Additionally, there is a notable lack of publications that evaluate uncertainty in standard analytical operations, such as dilutions, using the concept of NAP (maximum permissible variation in routine analysis), a principle endorsed by leading pharmacopoeias.

To bridge this gap, we conducted a PT round designed to estimate the criticality of risks within the context of pharmacopoeial standardization.

To the best of our knowledge, this study is the first to examine the impact of variation on the accuracy of decision-making regarding compliance with specifications for the standard analytical operation of aliquot sampling – widely recognized as the highest-risk step in dilution procedures. This was achieved by applying the concept of uncertainty, tailored to the specific requirements of pharmacopoeial standardization, while also considering the current skill levels of analysts. The evaluation focused on analyzing participants' performance in the following key areas: the determination of pipette-delivered volumes, adherence to GLP conditions, and the correctness of calculations. These aspects are discussed in detail below.

5. 1. Discussion of the results of determining the delivered volume

Discussion of the average deviation from the nominal value.

For 28 participants (44 %), the deviation from the nominal content is significant compared to U_{ISO}^{tg} (i.e., exceeds 0.01 mL×0.32=0.0032 mL or 0.16 %). This confirms the correctness of the chosen criterion *a*: $\overline{d_i} \le 0.010$ mL. Meeting the requirements for insignificance $\left(\overline{d_i} \le 0.0032 \text{ mL}\right)$ leads to more reliable results but is unachievable in practice for nearly half of the participants. On the other hand, the criterion $\overline{d_i} \le 0.010$ mL is practical based on the key requirements for personnel qualification.

Fig. 1 shows the distribution of $\overline{d_i}$ values in increasing order. It can be seen that the distribution is visually quite symmetrical relative to the nominal value (zero), indicating the randomness of the deviations, i.e., the absence of significant influence of systematic variation factors on the overall results of the participants.

The average value $\overline{d_i}$ for all participants is –0.0021 mL (–0.11 % of 2.0 mL). The median for $\overline{d_i}$ for all participants is –0.00026 mL (–0.013 % of 2.0 mL), thus meeting requirements (2). Both the average and median values deviate insignificantly (compared to $U_{ISO}^{tg} = 0.01$ mL or 0.5 %) from the nominal (certified) value. This confirms that the TI was

correctly certified, as the average result for all participants does not show a practically significant shift and aligns well with the median.

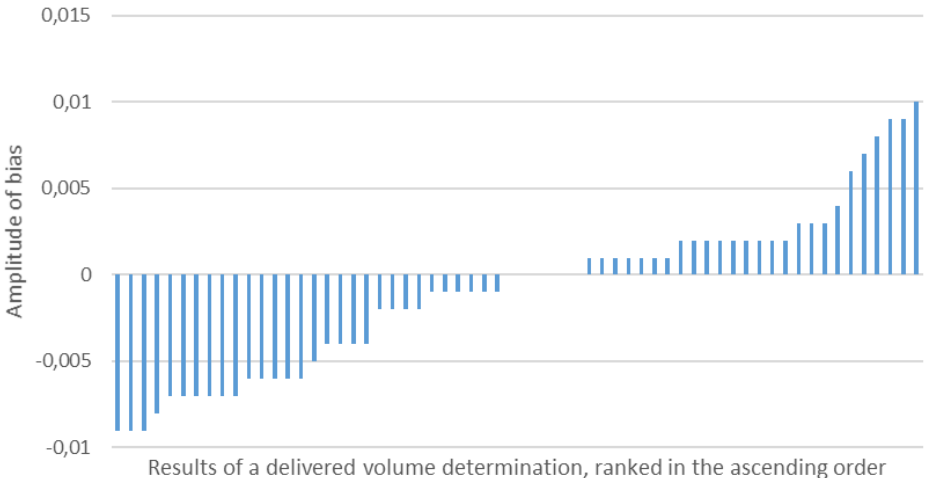

Fig. 1. Distribution of $\overline{d_i}$ (bias) values in increasing order

Three results that do not meet the requirements for participants under criterion *a* are simultaneously outliers by the 3s-criterion. Therefore, these data were excluded from the calculation of the metrological characteristics of the sample for $\overline{d_i}$. The standard deviation (SD)/relative standard deviation (RSD) for $\overline{d_i}$ is 0.0047 mL (0.23 %). The one-sided 95 % confidence interval (C.I.) for an individual value is 0.39 % and does not exceed the ISO requirement (0.5 %). Such a small C.I. indicates that, on average, analysts can reliably verify 2 mL pipettes in compliance with the ISO class A standard.

It can also be noted that the results obtained coincide with the recommendations of the Guide for evaluating uncertainty in the non-pharmaceutical sector [13]. Specifically, for volumetric glassware from a quality manufacturer, the average volume tends towards the nominal value; therefore, in assessing uncertainty associated with the use of volumetric glassware, a triangular distribution is usually applied to transition from error requirements to the value of standard uncertainty.

Discussion of individual deviations from the nominal value.

After excluding results of individual deviations that are burdened with gross error by the 3s-criterion, the average value $\overline{d_{ij}}$ amounted to –0.00085 mL (–0.043 %), and the median –0.00052 mL (–0.026 %). Thus, both the average value and the median insignificantly deviate (compared to $U^{tg}_{NAP} = 0.012$ mL or 0.61 %) from the nominal (certified) value and are very close to each other. This shows that the participants reliably meet the NAP requirements.

Discussion of the precision of participants' results.

The SD_i values of the participants are not homogeneous according to Cochran's criterion at the 95 % and 99 % confidence levels without excluding the non-compliant result and become homogeneous after excluding this result (SD_i=0.0083 mL, Laboratory 4, Analyst No. 3). Thus, the criteria for practical acceptability (requirements for participants) and statistical homogeneity at the significance levels of 95 % and 99 % indicate that the unacceptable participant`s result is an outlier.

After excluding the outlier, the root mean square value of SD is 0.00176 mL, which is almost two times less than the criterion. The difference between the SD_i requirements and the actual value of the participants can be assessed using Fisher's criterion:

$$F(v_1=4, v_2=228)=3.674,$$

$$P(F)=99\ \%,$$

where F is Fisher's criterion for the reliability level $P(F)$; v_1 is the number of degrees of freedom for repetitive measurements of volume (n=5) performed by each analyst; v_2 is the number of degrees of freedom for the total number of volume measurements by all analysts for a homogenous sample.

The difference between the root mean square value of SD_i and Fisher's criterion is highly significant (P=0.99), which means that all participants can reliably meet the *SD* requirements.

Discussion of correctness of decision on ISO compliance for volumetric glassware (parameter d).

Only one analyst (laboratory 9) received an incorrect result regarding the average delivered volume and did not provide a conclusion regarding the pipette's compliance with the ISO class A standard requirements. All other participants made the correct conclusion regarding the pipette's compliance.

General analysis of results.

Increasing the number of analysis results always leads to the appearance of values that deviate significantly from the certified value due to random variation factors (assuming the spread of results follows a Gaussian distribution). Following the SPhU approach [19], based on the binomial distribution, it is possible to calculate how many results may not meet the established criteria due to random variation for a given total number of analysis results. If the number of results that do not meet the criterion exceeds the calculated threshold for the chosen level of reliability, the non-compliance cannot be explained by random variation alone, indicating the need for corrective actions in the entire pharmaceutical sector. If the number of non-compliant results does not exceed the calculated threshold, corrective actions are only necessary for the laboratories whose results do not meet the requirements.

For a reliability level of 95 % (the generally accepted level in the pharmaceutical sector), out of 64 analysts who provided results, not more than 8 results (12.5 %) may not meet the requirements to consider such non-compliance as a result of random variation. Since the number of results that do not meet any criterion (*a–d*) is less than the critical number, the situation in the pharmaceutical

sector can be assessed as acceptable. Therefore, corrective actions are only needed for the laboratories from which non-compliant results were received. The planned corrective actions include discussing comments in PTS reports provided to participants, conducting a dedicated workshop on the PTS results, and specialized training on basic sample preparation operations by the USPCQM.

5. 2. Evaluation of the compliance of instruments and testing conditions with GLP

According to the Ph. Eur./SPhU requirements, glass volumetric glassware must meet ISO class A standards. Periodic verification of volumetric glassware compliance with established requirements (qualification) is one of the procedures for ensuring the quality of work in a testing laboratory. The test task procedure included requirements for the instruments necessary for calibrating volumetric glassware according to the ISO-4787 standard. The presence of such instruments and their compliance with established requirements are indicators of the laboratory's ability to qualify volumetric glassware and operate according to pharmacopeial requirements.

Therefore, participants were also asked to fill out a questionnaire aimed at clarifying compliance with GLP (the requirements of pharmacopoeias and other guidelines from authorities). Below is an analysis of the information provided by participants regarding their compliance with GLP.

Metrological verification/calibration and qualification of balances.

All participants, except for one laboratory, performed the test task using balances with a verification/calibration certificate from an authorized laboratory.

All participants provided information regarding the balance qualification, except for one laboratory. Based on a risk assessment, the testing laboratory independently established the parameters, acceptability criteria, and frequency of balance qualification. Analysis of the information provided by participants revealed that a significant number of laboratories (82 %) do not consider the OMCL guide recommendations [25] regarding the periodicity of Level IV (in-use instrument checks) balance qualification.

Parameters and metrological verification/calibration of thermometers.

All participants performed the test task using thermometers with a verification/calibration certificate from an authorized laboratory, except for one laboratory.

According to the test task conditions, water and air temperature measurements must be conducted using thermometers with a resolution≤0.1 °C and an expanded uncertainty of readings≤0.2 °C. Six laboratories worked with thermometers that did not meet the specified requirements.

Laboratory environment conditions.

According to the test task conditions, participants were required to ensure certain laboratory environment conditions (water temperature, air temperature, relative humidity, stability of conditions). Participants demonstrated compliance with the specified requirements except for the following:

– two laboratories did not meet the requirements for relative humidity;

– two laboratories did not meet the requirements for the difference between water temperature and air temperature during measurement.

Evaluation of the pipette's condition.

Before calibration and use, volumetric glassware must be checked for integrity and cleanliness. The analyst must be proficient in the criteria for evaluating the condition of the volumetric glassware, especially its cleanliness. Recommendations on this issue are provided in the ISO-4787 standard.

All participants evaluated the pipette's integrity, except for one laboratory. A significant number of laboratories (41 %) did not mention the evaluation of pipette cleanliness among the assessment parameters of its condition, with some of these laboratories washing the pipette before testing with detergents (degreasing agents), while others only rinsed it with the test liquid. Four laboratories showed the most thoroughness in assessing the cleanliness of the glassware.

General analysis of results.

It can be seen that for the following GLP requirements, the number of non-compliant conditions of analysis exceeded the specified criterion of 8 results or 12.5 %:

– metrological verification/calibration and qualification of balances (95 %);

– evaluation of the pipette's condition (41 %).

Thus, based only on these parameters, the situation is unacceptable for the pharmaceutical sector and requires training and testing of personnel across the entire sector. Therefore, the provider of the PT round proposed for all participants to undertake corrective actions [19].

5. 3. Evaluation of the correctness of calculations conducted by participants

Based on the provided primary data, the correctness of the calculations for the delivered volume and the *SD* was verified. The provider assessed the correctness of the data provision by calculating these parameters. The following problems were identified:

– errors in the calculations of the delivered volume (5 laboratories);

– errors in the calculations of the *SD* value (3 laboratories);

– incorrect rounding of results (either too low or too high) (7 laboratories).

Protocols from 52 % of analysts had problems regarding the correctness of calculations or rounding, indicating the necessity of corrective actions on this issue for the entire pharmaceutical sector [19].

Practical relevance. The findings indicate that corrective actions are necessary only for laboratories with non-compliant results. There is no justification for implementing corrective actions across the entire pharmaceutical sector.

The proposed test can be used to evaluate the proficiency of laboratory analysts through internal PT schemes, which is crucial to have evidence of the reliability of decisions about compliance with specifications

when reproducing procedures from pharmacopoeias or Marketing Authorization Dossiers [3, 17]. Consequently, it can serve as an analyst qualification test.

Research limitations. The proposed approach can be applied to studying the actual uncertainty of other standard operations, primarily dilutions using volumetric glassware (e.g., volumetric flasks). However, this approach cannot be extended to testing procedures involving burettes. Burettes are significantly more expensive compared to pipettes and volumetric flasks, making it impractical to provide all PT round participants with specially calibrated burettes as test items (TIs).

Prospects for further research. It can be assumed that PT round results reflect the best laboratory capability rather than a routine testing practice. In addition, PT providers inform participants about the acceptance criteria, thus encouraging participants to adjust results to fit them. Therefore, to accurately determine the uncertainty for the aliquoting operation under routine analysis conditions, it seems rational to organize a "blind" interlaboratory trial in which analysts are unaware that their results will be additionally evaluated for compliance with NAP requirements. This trial should ensure that the testing conditions closely resemble those of routine analysis. Unlike official participation in PT rounds, the results of the interlaboratory trial may not be reported to laboratory inspecting authorities, and the acceptance criteria are not communicated to the analyst. This approach relieves the pressure to obtain a result that satisfies the predefined acceptance criteria while allowing the assessment of the actual level of proficiency.

Furthermore, it would be interesting to develop procedures and conduct PT rounds to test personnel compliance with NAP requirements when using other volumetric glassware, e.g. volumetric flasks.

6. Conclusions

For the first time, components of the uncertainty for the individual standard analytical operation of taking an aliquot with a Mohr pipette were evaluated, and their compliance with the requirements of normal analytical practice was assessed to ensure the correct reproduction of the analytical procedure in other laboratories, comparability of analysis results between laboratories, and reliability in making correct decisions on compliance with specifications.

The testing procedure and acceptance criteria were developed based on ISO 4787 to assess participants' proficiency according to the key requirements for personnel qualification in routine quality control of pharmaceutical products. 95% of the participants obtained satisfactory results per the established acceptance criteria. The metrological characteristics of the results indicated that they could meet the requirements of normal analytical practice and perform pipette verification with high reliability, thereby complying with the key requirements for personnel qualification. The average results of all participants showed no significant bias or randomness in deviations from the nominal value, confirming the correctness of the certified value for the test item.

However, the analysts' systematic errors were significant compared to the ISO requirement for the delivered volume deviation from the nominal value (in our case, the certified value), confirming our earlier conclusion about the necessity to use a pipette with a certified delivered volume with acceptable uncertainty; verification of the pipette against ISO requirements alone is not sufficient. In addition, issues identified during the laboratory performance evaluation that pertain to incorrect calculations and rounding of results, qualification of balances, calibration of thermometers, laboratory environmental conditions, and the assessment of pipette condition indicate the necessity of personnel training and testing.

Statistical analysis of results indicates that corrective actions are necessary only for laboratories and analysts who obtained unsatisfactory results. These actions should focus on eliminating the analyst's non-compliance with the requirements of normal analytical practice. The pharmaceutical sector must address the non-compliance with GLP requirements through personnel training and testing.

The developed procedure can be used for personnel qualification in intra-laboratory proficiency testing schemes.

Conflict of interests

The authors declare that they have no conflict of interests in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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Data availability

Data will be made available at a reasonable request.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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