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Estimation of Measurement Uncertainty Using Top-Down and Bottom-Up Approaches for Accurate Content Determination of Meloxicam in Injectable Dosage Forms

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Abstract

Measurement uncertainty plays a critical role in ensuring the reliability, accuracy, and regulatory compliance of analytical results in pharmaceutical quality control. This study presents a comprehensive comparison of the Top-down and Bottom-up approaches for estimating the uncertainty associated with the quantitative determination of Meloxicam in injectable dosage forms using a validated HPLC method. The Top-down approach, based on method validation data, yielded an expanded uncertainty of ±0.336 mg per injection, while the Bottom-up approach (incorporating uncertainties from volumetric equipment, reference standards, and molar mass) produced a broader value of ±0.646 mg per injection. The results highlight the complementary nature of both approaches and support the integration of their respective strengths to improve the

robustness of uncertainty estimation. The proposed methodology is applicable to other methods within pharmaceutical quality control.

Key words: Bottom-up approach, meloxicam, measurement uncertainty, Top-down approach

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Introduction

Measurement uncertainty is a fundamental concept in analytical science, describing dispersion of values reasonably attributable to the measurand (1). It may arise from instrumental variability, environmental influences, or procedural inconsistencies (2). In pharmaceutical quality control, accurate measurement is essential to ensure that drug products meet predefined specifications for safety, efficacy, and quality (3). Estimating uncertainty clarifies the precision of a method, highlights areas for improvement (4), and, when variability is consistently high, signals inadequate process control or methodological flaws (3). Transparent reporting of uncertainty also builds confidence in analytical data by acknowledging potential limitations (5). For this reason, regulatory standards, such as ISO/IEC 17025:2017, require accredited laboratories to report measurement uncertainty, ensuring comparability of results across institutions (6).

Within method validation, measurement uncertainty serves as a key indicator of reliability under defined conditions. By quantifying the potential deviation of a result from the true value, it helps determine whether a method is fit for its intended purpose (7). Clear knowledge of the required precision facilitates the selection of appropriate methods and equipment, avoids unnecessary costs from excessive precision, and identifies cases where a method fails to meet precision requirements.

In pharmaceutical analysis, integrating rigorous method validation with comprehensive evaluation of measurement uncertainty provides a robust framework for generating reliable and traceable analytical data (7). The triad of precise measurement, validated methodology, and quantified uncertainty forms the cornerstone of regulatory compliance. To illustrate these principles in practice, the present study focuses on Meloxicam as the analyte of interest.

The objective of this study was to compare the measurement uncertainty of an in-house validated High-Performance Liquid Chromatography (HPLC) method for content determination of Meloxicam in injectable dosage forms (8) using both the Top-down and Bottom-up approaches. In the Top-down approach, uncertainty is estimated from method validation or routine quality control data, making it efficient and practical for established methods, though constrained by the scope of available performance data (9). By contrast, the Bottom-up approach quantifies individual sources of uncertainty at each stage of the measurement process. Although more labor-intensive, it provides a comprehensive profile and is particularly valuable during method development (10). Leveraging both approaches enables a more robust and holistic evaluation of measurement uncertainty in pharmaceutical analysis.

Ultimately, precision reflects the degree to which repeated measurements agree with each other, while reporting measurement uncertainty communicates the level of confidence in those results. Together, these elements are essential for ensuring the reliability, interpretability, and regulatory acceptability of analytical data. Without them, results risk being reduced to numbers without scientific value (11).

Materials and Methods

Chemicals, Solvents, and Instrumentation

All materials used for the development and validation of the method were of pharmaceutical grade. A Meloxicam reference standard (99.00% ± 0.08%) was kindly provided by Replek (Skopje). HPLC-grade acetonitrile (ROTISOLV, ≥99.9%, Carl ROTH) and in-house produced ultrapure water (TKA MicroPure-ST system) were used for the mobile phase, with pH adjusted using glacial acetic acid (≥99%, Sigma-Aldrich). Methanol (≥99.9%, Sigma-Aldrich) was used as the solvent for both standard and sample preparation.

The standard solution was prepared by dissolving approximately 20.0 mg Meloxicam reference standard in methanol in a 100.0 mL volumetric flask, sonicating for 20 min, and diluting to obtain 0.20 mg/mL. The sample solution was prepared by diluting 1.0 mL of Meloxicam injection (15 mg/1.5 mL) in a 50.0 mL volumetric flask with methanol, sonicating for 20 min, and adjusting to the same final concentration. Both solutions were filtered through 0.45 μm PTFE membrane filters prior to injection (8).

Analyses were performed on a Waters Alliance HPLC system (e-2695 separation module, Waters 2489 UV/Vis detector) with Empower 3 software and ApexTrack integration algorithm (8).

Applied Statistical Methodology

Measurement uncertainty was estimated according to the framework of the European Directorate for the Quality of Medicines & HealthCare (EDQM), which consists of four steps: (I) identification of the measurand, (II) identification of the uncertainty sources, (III) quantification of the uncertainty, and (IV) calculation of the combined standard and expanded uncertainties (12).

The first step consists of clearly defining the measurand, specifying its measurement unit and reporting format (13). The second step focuses on identifying all potential sources of uncertainty, often supported by an Ishikawa (fishbone) diagram for structured visualization and categorization (14). The third step consists of quantifying measurement uncertainty in line with the Quality Management (QM) documents issued by the EDQM, applying both the Top-down and Bottom-up approaches.

For the ***Top-down approach***, measurement uncertainty was estimated from method validation data, specifically intermediate precision and accuracy.

The relative standard uncertainty associated with the precision was calculated from intermediate precision data, according to the following equation (15):

$$Relative\ u(p) = \sqrt{\frac{(RSD_{BR})^2}{k} + \frac{(RSD_{WR})^2}{k \times n}} \qquad [1]$$

where: RSD_{BR} is the between-run RSD; RSD_{WR} is the within-run RSD (from one analyst); k is the number of analysts; n is the number of replicates per analyst.

The absolute standard uncertainty associated with the precision was then obtained using the following equation (15):

$$Absolute\ u(p) = Relative\ u(p) \times \bar{X} \qquad [2]$$

where $\bar{X}$ is the combined mean Meloxicam content obtained by both analysts.

The standard uncertainty related to accuracy was determined from analytical recovery data obtained across all concentration levels, using the following equation (15):

$$u(rec) = \frac{SD_R/100}{\sqrt{n}} \qquad [3]$$

A Student's *t*-test was performed to evaluate whether the mean recovery significantly deviated from the target value of 100%, and to determine whether bias correction was required. The standard uncertainty associated with bias was then calculated as (15):

$$u(b) = \sqrt{\frac{\sum_{i=1}^{q} b_i^2}{q}} \qquad [4]$$

where: q is the number of measurements; b_i represents either (I) the deviation of each recovery from 100%, or (II), in cases of statistically significant bias, the deviation from the mean recovery value.

For the ***Bottom-up approach***, measurement uncertainty was estimated from four components: the concentrations of the standard and sample solutions, together with the precision and accuracy of the method.

For the standard solution, the uncertainty was determined by considering the weighed mass of the reference standard, the volumetric flask used for dilution, and the molar mass of Meloxicam. The calibration of the analytical balance was performed using certified weights, and the associated uncertainty was calculated using constant and mass-dependent terms derived from the calibration. The uncertainty related to the declared purity (99.00% ± 0.08%, k = 2) was obtained directly from the certificate of analysis by dividing the stated uncertainty by the coverage factor (16). The uncertainty of the volumetric flask arose from calibration tolerance, repeatability, and temperature effects. Calibration uncertainty was modeled with a triangular distribution (16, 17), repeatability was assessed from ten replicate measurements of methanol mass, with volumes derived using its density (0.7913 g/mL), and thermal expansion was estimated for a ±4 °C variation around 20 °C using the volumetric expansion coefficient of methanol (0.00149 °C^{-1}) (18). The molar mass contribution was calculated from the molecular formula of Meloxicam ($C_{14}H_{13}N_3O_4S_2$) (19), using IUPAC atomic weights and their uncertainties treated with a rectangular distribution (20). The combined standard uncertainty of the standard solution concentration was then obtained by applying the root-sum-of-squares (RSS) method to the relative contributions of the weighed mass, volumetric flask, and molar mass (16, 21).

For the sample solution, uncertainty was derived from the pipette used to transfer the injection solution and the volumetric flask used for dilution. The same procedure was applied as for the standard solution, with adjustments based on nominal volumes and tolerances.

The uncertainty components related to the precision and accuracy of the method were already evaluated as part of the Top-down approach. To maintain consistency across both estimation approaches, these values were directly incorporated in the Bottom-up approach, ensuring methodological alignment and avoiding unnecessary duplication of calculations.

In the last step, the combined standard uncertainty was derived by applying the RSS method to all relevant components.

In the Top-down approach, the combined standard uncertainty was obtained from precision and bias (15):

$$u_c = \sqrt{u(p)^2 + u(b)^2} \qquad [5]$$

In the Bottom-up approach, the combined standard uncertainty was determined by including the uncertainties of the standard and sample concentrations, together with those from precision and bias (16, 21):

$$u_c = \sqrt{\left(\frac{u(C_{\text{Standard}})}{(C_{\text{Standard}})}\right)^2 + \left(\frac{u(C_{\text{Sample}})}{(C_{\text{Sample}})}\right)^2 + u(p)^2 + u(b)^2} \qquad [6]$$

The expanded uncertainty was calculated by applying an appropriate coverage factor to the combined standard uncertainty, as follows (15, 16, 21):

$$U = k \times (u_c \times \bar{X}) \qquad [7]$$

Results and Discussion

Identification of the Measurand

In accordance with the first step of measurement uncertainty estimation, the measurand was defined as the concentration of Meloxicam in the injection solution, expressed in mg/mL.

Identification of the Measurement Uncertainty Sources

In the second step, a fishbone diagram was constructed to systematically illustrate the principal sources of measurement uncertainty (Figure 1). Four categories were identified: those associated with the precision and accuracy of the method, and those associated with the concentration of the standard and sample solutions.

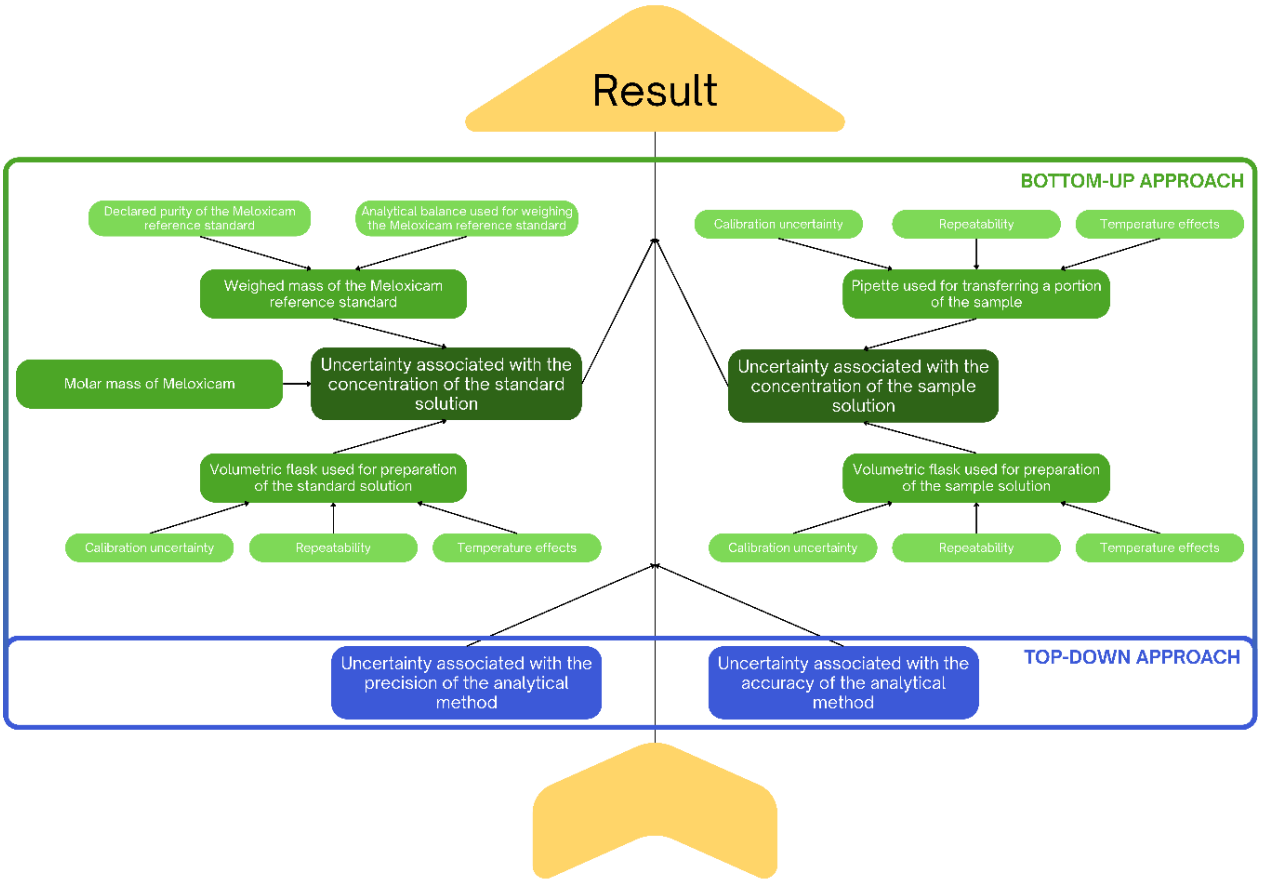

Figure 1. Sources of measurement uncertainty (Top-down and Bottom-up approaches)
Slika 1. Izvori merne nesigurnosti (odozgo nadole i odozdo nagore pristupi)

Uncertainties related to precision and accuracy were derived from method validation data, specifically intermediate precision and recovery experiments, and were treated as direct contributors in the Top-down approach. The Bottom-up approach incorporated these same parameters, but also expanded the model to include additional contributors arising from solution preparation. For the standard solution, these were the weighed mass (considering both the declared purity of the reference standard, and the performance of the analytical balance), the volumetric flask (with calibration limits, repeatability, and temperature effects), and the molar mass of Meloxicam. For the sample solution, uncertainty primarily originated from the pipette and volumetric flask used during preparation, reflecting calibration uncertainty, operational repeatability, and susceptibility to temperature-induced variations.

The sources summarized in Figure 1 were subsequently applied in the quantification step, forming the basis for the calculation of both the combined standard uncertainty and the expanded uncertainty.

Quantification of Measurement Uncertainty

Top-Down Approach

During method validation, intermediate precision was evaluated by two analysts, each performing six replicate analyses under repeatability conditions on the same day. The mean contents obtained were 101.19% for Analyst 1 and 100.89% for Analyst 2, with RSD values of 1.71% and 1.13%, and variances of 3.01 and 1.30, respectively (8).

Based on these results, the RSD_{BR} was calculated as 1.39%, while the RSD_{WR} was 1.13%. With $k = 2$ analysts and $n = 6$ replicates per analyst, substitution into Eq. 1 yielded a relative uncertainty associated with precision of 1.035% (0.01035). Combining the results of both analysts gave an overall mean content of 101.04%. Considering that each dosage unit contains 15.00 mg of Meloxicam in 1.5 mL of injectable solution, the mean content per dosage form was calculated to be 15.156 mg. Using Eq. 2, the absolute standard uncertainty associated with precision was determined to be 0.157 mg.

The standard uncertainty associated with accuracy was evaluated from recovery data obtained at three concentration levels, with three replicates each ($n = 9$). The recoveries ranged between 100.60% and 101.97%, with an overall mean of 101.26% and a standard deviation of 0.435% (8). By applying Eq. 3, the standard uncertainty related to recovery was calculated as 0.00145.

To assess whether the mean recovery differed significantly from the target value of 100%, a Student's *t*-test was performed. The calculated value ($t_{exp} = 8.69$) was compared with the critical value ($t_{crit} = 2.31$, 95% confidence level, $df = 8$). Since $t_{exp} > t_{crit}$, the deviation was statistically significant, indicating that bias correction was required. Accordingly, Eq. 4 was applied using the second approach, where each b_i represented the deviation of individual recoveries from the mean recovery.

Table I Calculation of b_i and b_i^2

Tabela I Proračun b_i i b_i^2

b_i	b_i^2
0.0014	0.00000196
–0.0003	0.00000009
–0.0011	0.00000121
0.0066	0.00004356
0.0051	0.00002601
–0.0011	0.00000121
0.0014	0.00000196
–0.0071	0.00005041
–0.0050	0.000025

The sum of squared deviations was 0.00015141, yielding a standard uncertainty associated with bias of 0.0041.

Bottom-Up Approach

The contribution of the weighed mass of the Meloxicam reference standard was first evaluated. The calibration of the analytical balance with certified weights gave an expanded uncertainty of 0.0533 mg. Dividing this value by the coverage factor (k = 2) yielded a standard uncertainty of 0.0267 mg.

The relative standard uncertainty of the weighed mass was 0.00133. In addition, the declared purity of the Meloxicam standard (99.00% ± 0.08%, k = 2) introduced a standard uncertainty of 0.04%, corresponding to a relative value of 0.000404.

By combining the contributions from mass and purity using the RSS method, the overall relative standard uncertainty of the weighed mass was obtained as:

$$\frac{u(m_{\text{Standard}})}{(m_{\text{Standard}})} = \sqrt{(0.00133)^2 + (0.000404)^2} = 0.00139$$

Expressed in absolute terms, this corresponded to 0.028 mg for the actual weighed mass of 20.14 mg.

The volumetric flask used for standard solution preparation had a nominal volume of 100.0 mL and a tolerance of ±0.1 mL at 20 °C. Due to the absence of information on coverage factor and confidence level, calibration uncertainty was modeled with a triangular distribution (15, 22), which resulted in a standard uncertainty of 0.0408 mL. The standard uncertainty from repeatability, based on ten consecutive measurements of methanol mass converted to volume, was 0.0444 mL.

The potential volume change due to temperature variation (±4 °C), applying the volumetric expansion coefficient of methanol (0.00149 °C^{-1}), was estimated to be 0.596 mL. Assuming a rectangular distribution across this interval (16–24 °C), the corresponding standard uncertainty was calculated as 0.344 mL.

By combining the calibration, repeatability, and temperature contributions using the RSS method, the combined standard uncertainty associated with the volumetric flask was 0.349 mL. The relative standard uncertainty was calculated as follows:

$$\frac{u(V_{\text{Standard}})}{(V_{\text{Standard}})} = \frac{0.349\ \text{mL}}{100.0\ \text{mL}} = 0.00349$$

Following the outlined methodology, the standard uncertainty associated with the molar mass of Meloxicam was evaluated using the atomic weights and associated uncertainties for each constituent element, as summarized in Table II.

Table II Atomic weight data and standard uncertainties for elements in Meloxicam

Tabela II Podaci o atomskoj masi i standardnim nesigurnostima za elemente u Meloksikamu

Element	Maximum atomic weight	Minimum atomic weight	Mean value	Range (±)	Elemental standard uncertainty
Carbon (C)	12.0116	12.0096	12.0106	±0.001	0.000577
Hydrogen (H)	1.00811	1.00784	1.007975	±0.000135	0.0000779
Nitrogen (N)	14.00728	14.00643	14.006855	±0.000425	0.000245
Oxygen (O)	15.99977	15.99903	15.9994	±0.00037	0.000214
Sulfur (S)	32.076	32.059	32.0675	±0.0085	0.00491

Based on these values, the molar mass of Meloxicam was calculated as 351.405 g/mol. The elemental variances were then combined using the RSS method, as shown in Table III.

Table III Contribution of elemental standard uncertainties to the standard uncertainty of Meloxicam's molar mass

Tabela III Doprinos standardnih nesigurnosti elemenata ukupnoj standardnoj nesigurnosti molarne mase Meloksikama

Element	No. of atoms (n)	Elemental standard uncertainty (u)	u^2	$n \times u^2$
Carbon (C)	14	0.000577	0.000000333	0.00000466
Hydrogen (H)	13	0.0000779	0.00000000607	0.0000000789
Nitrogen (N)	3	0.000245	0.00000006	0.00000018
Oxygen (O)	4	0.000214	0.0000000458	0.000000183
Sulfur (S)	2	0.00491	0.0000241	0.0000482

The total combined variance was 0.0000533, yielding a standard uncertainty of 0.0073 g/mol. The relative standard uncertainty of the molar mass was calculated as follows:

$$\frac{u(M_{\text{Meloxicam}})}{M_{\text{Meloxicam}}} = \frac{0.0073\ \text{g/mol}}{351.405\ \text{g/mol}} = 0.0000208$$

Consequently, the relative standard uncertainty associated with the concentration of the standard solution was calculated as:

$$\frac{u(C_{\text{Standard}})}{(C_{\text{Standard}})} = \sqrt{(0.00139)^2 + (0.00349)^2 + (0.0000208)^2} = 0.00375$$

Accordingly, the concentration of the standard solution was calculated as:

$$C_{\text{Standard}} = \frac{20.14\ \text{mg} \times 0.99}{100\ \text{mL}} = 0.199386\ \text{mg/mL}$$

By multiplying this value with the relative standard uncertainty, the absolute standard uncertainty was determined to be 0.000748 mg/mL.

The uncertainty associated with the concentration of the sample solution was evaluated from the volumetric equipment used in its preparation, namely the 1.0 mL pipette (tolerance of ±0.006 mL at 20 °C) and the 50.0 mL volumetric flask (tolerance of ±0.06 mL at 20 °C). Applying the same statistical model as for the standard solution, the combined standard uncertainties were 0.0177 mL for the pipette and 0.182 mL for the flask, corresponding to relative uncertainties of 0.0177 and 0.00364, respectively. By combining these contributions, the overall relative standard uncertainty of the sample solution concentration was 0.0181. For a working concentration of 0.20 mg/mL, this gave an absolute standard uncertainty of 0.00362 mg/mL.

Calculating the Combined Standard and Expanded Uncertainties

In the Top-down approach, the combined standard uncertainty obtained from precision and bias was calculated according to Eq. 5, giving a value of 0.0111 (1.11%). Using Eq. 7 with a coverage factor of k = 2 (95% confidence level), the expanded uncertainty was determined as 0.336 mg. Since the mean recovery deviated significantly from the target value of 100%, the mean content was corrected for bias, resulting in a final mean of 14.967 mg. Consequently, the Meloxicam content, expressed with expanded uncertainty, was 14.967 ± 0.336 mg per injection, corresponding to an interval of 14.631–15.303 mg with a 95% confidence level (k = 2).

In the Bottom-up approach, all relevant contributors were included, namely the concentrations of the standard and sample solutions together with method precision and bias. The combined standard uncertainty was obtained by applying Eq. 6, yielding 0.02156 (2.156%). Applying Eq. 7 again with k = 2 (95% confidence level) gave an expanded uncertainty of 0.646 mg. Thus, under this approach, the final result was 14.967 ± 0.646 mg per injection, corresponding to an interval of 14.321–15.613 mg with a 95% confidence level (k = 2).

Conclusion

The present study demonstrated the successful application of both Top-down and Bottom-up approaches for the estimation of measurement uncertainty in the content determination of Meloxicam in injectable dosage forms by HPLC. The Top-down approach offered a pragmatic and efficient estimation based on validation data, while the Bottom-up approach provided a more comprehensive analysis by incorporating uncertainties from all analytical stages. The broader uncertainty observed with the Bottom-up approach reflects its inclusive nature. Importantly, the application of both approaches demonstrated that the obtained results, including their associated

measurement uncertainties, remained within the regulatory specification limits of 95.0–105.0% of the declared content. Even in hypothetical borderline scenarios, the expanded uncertainty intervals calculated in this study would not extend beyond the specification limits, indicating that the method provides a scientifically reliable basis for regulatory acceptance.

In the context of analytical method validation, the Top-down approach is generally more appropriate, as it directly derives the uncertainty estimates from the method's own validation data. The Bottom-up approach, while conceptually rigorous, is not always the most practical choice in this setting, because when the original analytical method is reproduced in another laboratory, it cannot be assumed that identical volumetric equipment, sample material, or a reference standard from the same manufacturer will be used. Consequently, the calculated measurement uncertainty directly influences regulatory acceptance, particularly when results lie close to specification limits. Therefore, there is an increasing tendency for measurement uncertainty to become an integral component of validation protocols to ensure regulatory acceptability.

These findings highlight that, although the Top-down approach is the most suitable and practical choice for routine analytical method validation, the Bottom-up approach remains valuable as a complementary tool, offering a deeper understanding of the individual sources of uncertainty. When used together, the two approaches provide a balanced, traceable, and scientifically defensible estimation of measurement uncertainty. The integrated use of both approaches therefore strengthens the reliability of the uncertainty assessment and supports laboratories in meeting regulatory requirements and ensuring data integrity in pharmaceutical analysis.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

DK: Conceptualization, Formal analysis, Investigation, Visualization, Writing – original draft; IM: Conceptualization, Methodology, Validation, Writing – review & editing; PA: Investigation, Visualization; MA: Investigation; ZAS: Methodology, Writing – review & editing; MDS: Writing – review & editing; BD: Writing – review & editing; JTR: Writing – review & editing; BG: Project administration.

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Procena merne nesigurnosti primenom pristupa odozgo nadole i pristupa odozdo nagore za tačno određivanje sadržaja meloksikama u injekcionim farmaceutskim oblicima

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Kratak sadržaj

Merna nesigurnost ima ključnu ulogu u obezbeđivanju pouzdanosti, tačnosti i regulatorne usklađenosti analitičkih rezultata u okviru kontrole kvaliteta farmaceutskih proizvoda. Ova studija predstavlja sveobuhvatno poređenje pristupa odozgo nadole (*Top-down*) i odozdo nagore (*Bottom-up*) u proceni nesigurnosti povezane sa određivanjem sadržaja meloksikama u injekcionim farmaceutskim oblicima, primenom validirane HPLC metode. Merna nesigurnost izračunata primenom pristupa odozgo nadole koji je zasnovan na podacima dobijenim tokom validacije metode, iznosi ±0,336 mg po injekciji. Primenom pristupa odozdo nagore, koji uključuje pojedinačne doprinose nesigurnosti od volumetrijske opreme, referentnih standarda i molarne mase, dobijena je viša vrednost od ±0,646 mg po injekciji. Dobijeni rezultati ukazuju na komplementarnost ovih pristupa i sugerišu da njihova integracija može doprineti unapređenju robusnosti procene nesigurnosti. Predložena metodologija ima potencijal za primenu i u drugim analitičkim metodama u okviru kontrole kvaliteta farmaceutskih proizvoda.

Ključne reči: pristup odozdo nagore, meloksikam, merna nesigurnost, pristup odozgo nadole