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Determination of uncertainty measurement using top-down approach and its correlation towards Total Error (TE) on hematology parameter

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Abstract

Background: Uncertainty Measurement (UM) is defined as a parameter associated with a measurement result that characterizes a dispersion of values that can reasonably be associated with a quantity. ISO 15189 clause 5.5.1.4. states that the laboratory shall determine measurement uncertainty for each measurement procedure in the examination phase used to report measured quantity values on patients samples. *Objectives:* According to Westgard, there is debate about difference between the concepts of Uncertainty and Total Error (TE) so this study was conducted which aims to determine the uncertainty value of hematological parameters and determine the correlation of Uncertainty and TE. *Materials and Methods:* The material in this research are data of Internal Quality Control (IQC), External Quality Control (EQC), and Uncertainty data from the Sysmex XN-1000 calibrator. *Results:* Through the results the average uncertainty value of Sysmex XN-1000 2022 for leukocyte with low, medium and high levels, are ±19.05%, ±18.07 %, and ±15.94%, while for erythrocyte are ±4.46%, 4.10%, 4.16%, for hemoglobin are ±5.63, ±5.07, ±5.01, for hematocrit are ±8.99%, ±8.19%, ±8.19%, and for platelet are ±79.23%, ±62.23%, ±58.29%. *Conclusions:* Based on the uncertainty and TE calculated permonth for each lot number during 2022, the correlation was obtained between the Uncertainty and TE among leukocyte and hematocrit were stated to have a weak correlation, for hemoglobin and platelet it was stated quite correlated and erythrocytes are stated to be strongly correlated.

Keywords

Correlation, Top-down approach, Total Error, Uncertainty

1. Introduction

Uncertainty is defined as a parameter associated with a measurement result that characterizes the dispersion of values that can reasonably be attributed to a quantity. By quantifying variations in results, both the clinical laboratory carrying out the measurements and those receiving the results can have an objective estimate of the quality of the results (Sari, Rusmiati, et al. 2018). Measuring uncertainty in laboratory examinations is one of the scopes of documented procedures for

equipment calibration which is part of traceability, this is stated in ISO 15189:2012.

ISO 15189:2012 clause 5.5.1.4. about Measurement Uncertainty of Measured Quantity Values states that laboratory shall determine measurement uncertainty for each measurement procedure in the examination phase used to report measure quantity values on patients' samples. Measurement uncertainties may be calculated using quantity values obtained by the measurement of quality control materials under intermediate precision conditions that include as many routine changes as reasonably possible in the standard operation of a measurement procedure e.g. changes of reagen and calibrator batches, different operators, scheduled instrument maintenance.

The "top-down" approach directly estimates measurement uncertainty typically by evaluating quality control (QC) data or method verification experimental data. A "top-down" approach is more practical and cost-effective, able to be updated as further data becomes available through results from routine Internal Quality Control (PMI) and External Quality Control (PME) or proficiency testing (UP). The results show that no statistically significant differences were found between the uncertainty values obtained with both top-down and bottom-up approaches (Martinello, Snoj, Skitek, & Jerin, 2020)

2. Materials and Methods

The material in this research are data of Internal Quality Control (IQC), External Quality Control (EQC), and Uncertainty data from the Sysmex XN-1000 calibrator at Balai Laboratorium Provinsi Jawa Barat. The sample used is secondary data using a total sampling technique taken during 2022. PMI data is used as a source of standard uncertainty (Urw) which comes from impressions, while PME data is used for bias uncertainty (Ubias) and calibrator uncertainty data for uncertainty calibrator (Ucal). The PME which was attended by the hematology field at the West Java Provincial Health Laboratory Center for the Sysmex XN-1000 instrument was organized by Biorad.

The approach used is the top-down method stated in a number of documents including the Eurachem/CITAC Guide: the Eurolab report on alternative approaches to uncertainty evaluation and ISO 20914: 2019 concerning Calculation of Uncertainty. Here is the following are the data processing steps:

2.1. Data Processing

2.1.1. Measurement of Standard Deviation (SD) and Coefficient of Variation(%CV)

1) After the results of the internal QC data are obtained, for each parameter the average value

(mean) of the internal QC data is calculated every month at a minimum of 2 QC levels using Ms. Excel with the formula "=AVERAGE (number1;number2;…)". Number 1 and number 2 are daily internal QC data obtained.

2) Standard Deviation (SD) of internal QC results data every month at a minimum of 2 QC levels is calculated using Ms. Excel with the formula "=STDEV (number1;number2;…)". Number 1 and number 2 are daily internal QC data obtained. The equation can be explained as follows:

$$SD = \{[(SD)_{L1}{}^2 + (SD)_{L1}{}^2]/\ 2\}^{1/2} \text{ .....(1)}$$

$(SD)_{L1}$ and $(SD)_{L1}$ = average standard deviation of each control level, each for the last 1 year

3) If more than two levels are used in the QC requirements and clinical decision limits for that method, calculate the mean SD as follows:

$$SD = \left[(n_1 SD_1{}^2 + n_2 SD_2{}^2 + \cdots n_x SD_x{}^2\right)/\ (n_1 + n_2 + \cdots n_x)^{1/2} \text{..... (2)}$$

4) Once the average and SD values are known, the coefficient of variation (CV%) value is calculated by dividing the SD value by the average value and then multiplying by 100, as in the following formula:

$$CV = \frac{SD}{\bar{x}} x100 \text{ .....(3)}$$

CV = Coefficient of Variation

SD = Standard Deviation

$\bar{x}$ = Average of control material inspection results

2.1.2. Measurement Bias (d%)

1) Calculate bias related to the method, namely bias from calibrator and interlaboratory data.
2) For data taken from peer group results from the EQAS program each month, it is used as the Target Value(TV) in bias calculation (d%)
3) The average value that has been calculated each month is also used to calculate bias (d%) using the following formula:

$$d\% = \frac{(\bar{x} - TV)}{TV} x100 \text{ .....(4)}$$

$\bar{x}$ = average of control material inspection results

TV = Target Value

2.2. Data analysis

2.2.1. Calculation of Standard Uncertainty (Urw)

Standard uncertainty (Urw) is the average value of the impression (standard deviation) obtained in

long term precision measurements (Magnusson, Naykki et al., 2014)

$$\text{Urw} = \frac{\Sigma SD}{\bar{x}} x100 \text{ ..... (5)}$$

Urw = Standard uncertainty

ΣSD = Standard Deviation each month

$\bar{x}$ = Average of control material inspection results

2.2.2. Bias Uncertainty Calculation (uBias)

Calculation of bias uncertainty can be done using data from Certified Reference Material (CRM), EQAS, and Interlaboratory Internal Quality Control Scheme (IQCS) sources (Martinello, Snoj et al., 2020). In the bias that comes from EQAS, the examination results are compared to the average value of the peer group as the target value.

$$d\% = \frac{(\bar{x} - TV)}{TV} x100 \text{ ..... (6)}$$

$\bar{x}$ = EQAS sample inspection results

TV = Target Value from the average results of the EQAS peer group

If the bias is corrected with Certified Reference Material (CRM) it is as follows (ISO 20914, 2019):

$$Ubias = \sqrt{(u^2 ref + SD^2 mean)} \text{ ..... (7)}$$

Uref = standard uncertainty of certified reference materials/calibrators

SD^2_{mean} = the average value of the reference material obtained under repeated conditions

The calculated standard uncertainty (SDmean) is the average value of the control material obtained repeatedly, the value is obtained using the following equation:

$$\text{SDmean} = \frac{\text{SD}}{\sqrt{\text{n}}} \text{ ..... (8)}$$

SD = standard deviation of replicate measurements of reference material

n = number of obtained values

2.2.3. Overall Standar Measurement Uncertainty U(y) Calculation

The calculation of the combined uncertainty U(y) if there is bias uncertainty and uncertainty originating from the calibrator is as follows:

$$\text{U(y)} = \sqrt{(u_{bias}^2 + u_{cal}^2 + u_{rw}^2)} \text{ ..... (9)}$$

U(y) = Overall standard measurement uncertainty

Ucal = Uncertainty of value assigned to calibrator

Ubias = Uncertainty of any bias correction

Urw = impression of the measurement procedure under long-term precision condition

If bias is ignored and there is only calibrator and impression uncertainty from the IQC data, the combined uncertainty is as follows:

$$U(y) = \sqrt{(u_{cal}^2 + u_{rw}^2)} \quad \text{..... (10)}$$

If bias is ignored and there is no calibrator uncertainty then the impression value or Urw = SD = combined uncertainty U (y) associated with the results:

$$U(y) = \sqrt{u_{rw}^2} \quad \text{..... (11)}$$

2.2.4. Expanded Uncertainty Calculation (U)

Calculating Extended Uncertainty (U)

$U = U(y) \times k$

$U = U\ (y)\ x\ 1.96\ (\sim 2)$

K= coverage factor with confidence level 95%

2.2.5. Calculation of Total Error (TE)

After obtaining the coefficient of variationand bias, calculations are carried out to determine the Total Error using the formula:

$$Total\ Error = \%Bias + 2CV\% \quad \text{.....(12)}$$

3. Results and Discussion

3.1. Results

Based on the research results through the data obtained, Uncertainty calculations can be carried out using the ISO/TS 20914:2019 algorithm so that the estimated uncertainty values for hematological parameters in 2022 for each level are obtained as follows Table 1.

To determine a clinically acceptable Uncertainty target for each analyte, you can compare the value against Biological Variation (BV). The recommendation for the use of BV is based on a large linear relationship between biological and analytical variations that leads to limits for laboratory

examination (Haeckel, Wosniok et al., 2015). The BV amount is multiplied by a fixed factor so that the permissible limits will be too strict for relatively small biological variations and too large for relatively large biological variations so that until now the science regarding calculating Uncertainty tolerance limits is still developing.

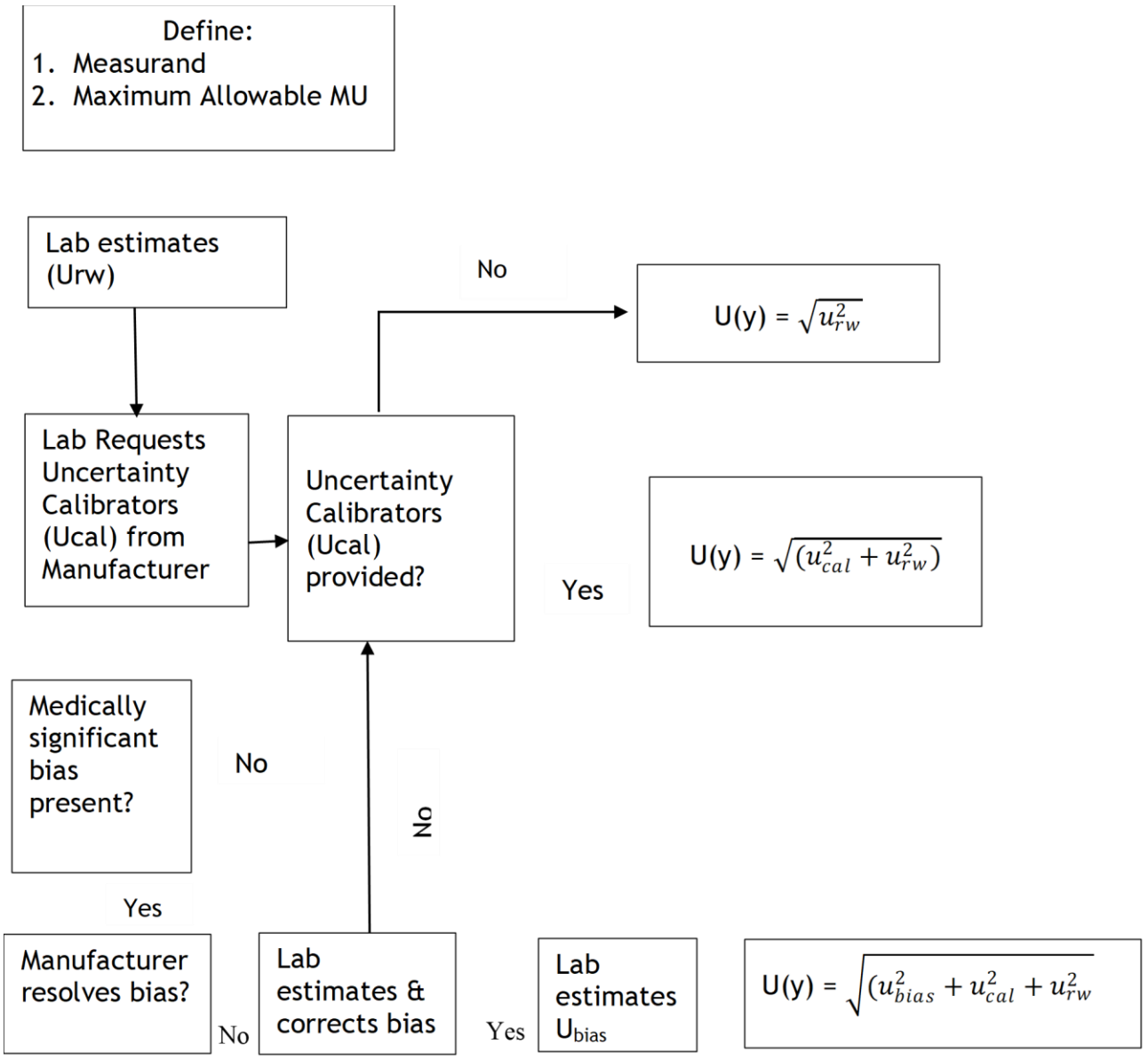

Figure 1. Overview of typical pathway for estimating measurement uncertainty with reference to specific worked ISO/TS 20914:2019

Table 1. Table of average uncertainty values for Hematology Parameters in 2022

Parameters	The Average Uncertainty			BV
	Low	Normal	High	%
Leukocytes	19.0	18.1	15.9	14.6
Erythrocytes	4.5	4.1	4.2	4.4
Hemoglobin	5.6	5.1	5.0	4.1
Hematocrit	9.0	8.2	8.2	4.1
Platelets	79.2	62.6	58.3	13.4

After obtaining the Uncertainty and Total Error (TE) values, a statistical test was carried out to determine the correlation. The type of correlation test is determined through a normality test carried out on all data during 2022 and it is concluded that the data distribution is not normal, this is because there is a large amount of data in each parameter which is considered an outlier because the data is too widely spread because the data is used for a full year, the test used to carry out correlation is the Spearman Test.

In determining the level of strength of the correlation relationship between Total Error (TE) and Uncertainty, it can be seen from the correlation coefficient value with the following conditions:

Table 2. The correlation coefficient interpretation

Correlation coefficient	Interpretation
0.00 – 0.25	The correlation is very weak
0.26 – 0.50	Correlation is sufficient
0.51 – 0.75	Strong correlation
0.76 – 0.99	The correlation is very strong
1.00	Perfect correlation

The basis for drawing conclusions from the Correlation Test is by looking at the significance value, where if the significance value is <0.05 then it is correlated and if the significance value is >0.05 then it is not correlated.

Table 3. Correlation Test of Total Error (TE) and Uncertainty of Hematological Parameters (n=48)

Leukocytes	**Correlation Coeffisient**	**0.236**
	Sig (2-tailed)	0.107
Erythrocytes	Correlation Coeffisient	0.591
	Sig (2-tailed)	0.000
Hemoglobin	Correlation Coeffisient	0.494
	Sig (2-tailed)	0.000
Hematocrit	Correlation Coeffisient	0.253
	Sig (2-tailed)	0.083
Platelets	Correlation Coeffisient	0.411
	Sig (2-tailed)	0.004

Through the Spearman test, the results obtained show that the correlation coefficient depends on the significance value, where if the significance value is <0.05 then it is correlated and if the significance value is >0.05 then it is not correlated. Significance values for Total Error (TE) and Uncertainty for leukocyte and hematocrit parameter between the range 0.00 – 0.26 which can be interpreted as a weak correlation so that it can be concluded that the relationship between Total Error (TE) and Uncertainty in the leukocyte and hematocrit parameters is very weakly correlated. Meanwhile, for the hemoglobin and platelet parameters, correlation coefficient values were obtained in the range 0.25 - 0.50, which is quite correlated, and erythrocyte parameters were in the range 0.51 - 0.75, which is strongly correlated.

3.2. Discussion

The Total Error (TE) approach identifies systematic error (bias) and random error (impression) as two components of total measurement error. Bias is the predictable offset of a result from a reference value, usually estimated as the difference between the reference value and the average result obtained when the reference is measured in replicates by a routine measurement procedure.

The magnitude of the inaccuracy/bias cannot be predicted for each measurement result produced by the test, due to factors such as fluctuations in electromechanical performance, batch changes reagents and calibrators, different operators, routine instrument maintenance. Impression is usually estimated by measuring a control material in different analytical runs spread over sufficient time to incorporate as many of the above routine changes in measurement conditions as possible. The TE concept describes the total error of a measurement system as TE = Bias + 2 SD, where 2 SD represents ~95% dispersion of the results obtained on one side of an imprecise Gaussian curve.

In contrast to TE, Uncertainty has no effect on the estimated measurement error. Routine laboratories generally measure patient samples once rather than multiple times, and therefore the Uncertainty approach focuses on identifying the spread of results that might be obtained for an analyte if the sample had been measured repeatedly rather than once. To do this, the Uncertainty approach uses available data on repeated measurements of a given measurement system to determine the value interval within which the true value of the measured analyte (Westgard, 2021). Uncertainty does not estimate error, but provides a quantitative estimate of where the true value of the measured analyte is believed by the laboratory to lie, with a stated level of confidence. Uncertainty calculations with a Top-down approach directly estimate measurement uncertainty usually by evaluating quality control (QC) data or method verification experimental data. A "top-down" approach is more practical and cost-effective, able to be updated as further data becomes

available through results from routine Internal Quality Control (PMI) and External Quality Control (PME) or proficiency testing (UP). The results show that no statistically significant differences were found between the uncertainty values obtained with both top-down and bottom-up approaches (Martinello, Snoj, Skitek, & Jerin, 2020).

The calculation of uncertainty values or Uncertainty using the Top-down method consists of Standard Uncertainty (Urw), Bias Uncertainty (Ubias) and Calibrator Uncertainty (Ucal). The Urw value is obtained from impressions of Internal Quality Control (PMI) control data, while Ubias can come from Certified Reference Material (CRM), EQAS, and Interlaboratory Internal Quality Control Scheme (IQCS) sources (Martinello et al., 2020).

Uncertainty comes from impression, bias and calibrator uncertainty, followed by the calculation of Combined Uncertainty or U(y). The U(y) value obtained is then multiplied by a coverage factor of 2 for laboratories with a confidence level of 95% to obtain an expanded Uncertainty value (U). All the main sources leading to the spread of combined uncertainty are the combined uncertainty ± quantitatively measured values (Milinkovic, Ignjatovic et al., 2018).

Calibrator Uncertainty (Ucal) can be obtained from the Calibrator Uncertainty certificate when calibration has been carried out. In the uncertainty calculations carried out, Ubias is obtained from EQAS data which is followed every month by the Bandung Provincial Health Laboratory Center for the Sysmex XN-1000 tool, which is held by Biorad. Bias means a predictable offset value relative to an appropriate reference, for example the value determined from Certified Reference Material (CRM) or the EQAS value obtained against the peer group average. Whatever approach is used to determine bias values for routine measurement procedures, the Uncertainty approach assumes that known biases can be eliminated or minimized for example by recalibration.

Calculations can be used to calculate the uncertainty of a laboratory result because it is a more influential factor than repetition and day to day variation. This is due to the quality of reagents, systems and procedures which continue to be improved thereby reducing repeatability and day to day variation, so that they can dominate (Theodorson, 2014).

Through the results obtained and compared to BV, the leukocyte parameters at low, normal and high levels all three exceed the TEa limit determined by BV, for the erythrocyte parameters at normal and high levels they are less than TEa but at low levels they exceed the TEa limit value. In the parameter's hemoglobin, hematocrit and platelets, the average uncertainty value in 2022 at all three levels exceeds the TEa limit determined by BV. The average value of uncertainty in platelets is of concern because it is very far from the range determined by BV.

The cause of uncertainty results in parameters that have very high values is due to the source of

the uncertainty calculation itself including standard uncertainty (Urw) which comes from impressions, bias uncertainty (Ubias) and calibrator uncertainty (Ucal). It can be seen in the uncertainty results with low control that all parameters are above the limit is determined by BV%, this is because at low concentrations the impression tendency obtained is higher so that higher CV results are obtained. Test precision is declared acceptable if SD or CV < 0.33% TEa(Brooks, 2001).

In the Leukocyte parameter, the average uncertainty value for 2022 at the three levels above the %BV limit is 14.6. The reason this occurs is due to the monthly Uncertainty data parameters listed in the research results in table 4.3. calculation of leukocyte parameter uncertainty, obtained in January, May, July, September and November > %BV.

In the Erythrocyte parameters, the average uncertainty value in 2022 is at a low level above the %BV limit which is 4.4%. The reason this occurs is because of the monthly Uncertainty data for the parameters listed in the research results in table 4.5. calculation of erythrocyte parameter uncertainty, obtained in July, October, November and December > %BV. In July and October, Uncertainty Bias values were obtained that exceeded the limit > BV (BA% = 1.7). Biased data reflects systematic errors so that it can be stated that in that month there were consistent variations or deviations that caused significant changes in accuracy (average value to actual value).

For the parameters hemoglobin, hematocrit and platelets, the average uncertainty value in 2022 is obtained at the three levels above the %BV limit of each parameter, this is due to U(y) or the combined uncertainty of the calibrator uncertainty, standard uncertainty and bias uncertainty in the parameters The results obtained tend to be large, especially in platelet parameters. Therefore, the Australasian Association of Clinical Biochemists Uncertainty of Measurement Working Group (AACB) Guidelines recommend that whatever approach is used to determine the bias value for routine measurement procedures so that the bias value is obtained, it should be eliminated in the calculation or minimized, for example by recalibration. Another alternative is that the bias value is corrected by carrying out measurements on the Certified Reference Material (CRM) which are carried out repeatedly using the following formula (ISO 20194:2019):

$$Ubias = \sqrt{(u^2ref + SD^2mean)} \quad \text{..... (13)}$$

U^2_{ref} = standard uncertainty of certified reference materials/calibrators

SD^2 mean = average value of reference material obtained under repeated conditions

SD_{mean} is the average value of the control material obtained repeatedly, the value is obtained using the following equation:

$$SD_{mean} = \frac{SD}{\sqrt{n}} \text{ ..... (14)}$$

SD = standard deviation of repeated measurements of control material

n = number of control levels used each month

After obtaining the Uncertainty and Total Error (TE) values, a statistical test was carried out to determine the correlation. The type of correlation test is determined through a normality test carried out on all data during 2022 and it is concluded that the data distribution is not normal, this is because there is a large amount of data in each parameter which is considered an outlier because the data is too widely spread because the data is used for a full year, so the test used to carry out correlation is the Spearman Test.

Through the Spearman test, the results showed that the correlation coefficient between Total Error (TE) and Uncertainty in the leukocyte and hematocrit parameters was between the range 0.00 – 0.26, so it can be concluded that the relationship between Total Error (TE) and Uncertainty in the leukocyte and hematocrit parameters is very weakly correlated. Meanwhile, for the hemoglobin and platelet parameters, correlation coefficient values were obtained in the range 0.25 - 0.50, which is quite correlated, and erythrocyte parameters were in the range 0.51 - 0.75, which is strongly correlated.

Only erythrocyte parameters obtained strong correlated results and if compared with the uncertainty and total error (TE) values of erythrocytes, these parameters have quite good values because there is no TE that exceeds the Total Error Allowable (TEa) value and the uncertainty value obtained for the level normal and high controls are quite good because they are below the %BV value. Unlike other parameters whose uncertainty value exceeds the %BV value, conclusions can be drawn for the correlation test between Uncertainty and Total Error which is determined by the magnitude of the Uncertainty and TE values for each parameter so further research should be carried out regarding the evaluation of the Uncertainty value against Total Error (TE).

The underlying reason for the difference between TE and Uncertainty is that Total Error provides an estimated evaluation value for the total error of the measurement system and TE is useful for determining the permitted error limits, whereas Uncertainty does not estimate the total measurement error but rather estimates the value interval in which the actual value of the analyte being measured believed to be with the stated level of confidence. Known significant bias should be eliminated or minimized, and the bias reassessed in terms of the uncertainty of the bias values

used for recalibration or correction of results (Westgard, 2021).

Basically, the Uncertainty value will increase if the traceability chain moves down. The further along the traceability chain, the uncertainty will increase, so the laboratory is tasked with ensuring that the measurement results do not widen further so that the ideal Uncertainty value obtained for all parameters is as small as possible. Best Measurement Capability is the smallest uncertainty that can be achieved by a laboratory within the scope of its accreditation in carrying out routine calibration activities of measurement standards so that it can approach the ideal value used to define, realize, maintain or reproduce a unit of that measuring quantity.

4. Conclusions

Based on the results of research that has been carried out to determine Uncertainty estimates using the Top-down method and its correlation with the Total Error (TE) value on the Hematology Parameters of the Sysmex -1000 during the 2022 period for control leukocyte parameters low level ±19.05%, normal ±18.07%, high ±15.94%, then control erythrocyte parameters low level ±4.46%, normal ±4.10%, high = ±4.16%, hemoglobin level parameters control low ±5.63%, normal ±5.07%, high = ±5.01%, for hematocrit parameters control level low ±8.99%, normal ±8.19%, high ±8.19%, and platelet parameters control level low ±79.23%, normal ±62.23 %, high ±58.29%. The correlation relationship obtained between the Uncertainty and Total Error (TE) values, among others, is that the leukocyte and hematocrit parameters are stated to be weakly correlated, and the hemoglobin and platelet parameters are stated to be quite correlated and the erythrocyte parameters are stated to be strongly correlated so that it can be stated that Total Error and Uncertainty are two aspects that complement each other, but have different measurement characteristics and the correlation test between Uncertainty and Total Error for each parameter is determined by the magnitude of the Uncertainty and TE values for each parameter.

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