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# The instability of commercial control materials in quality control of mean corpuscular volume

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ABSTRACT

*Background:* Mean corpuscular volume (MCV) of stabilized whole blood used for quality control (QC) of hematology analyzers exhibits a tendency to increase during storage. The aim of this study is to evaluate the extent of biases over time with 3 most widely used control materials and to map out a strategy to overcome the data shift of MCV on daily QC practice.
*Methods:* QC results of TESTPoint tested by ADVIA 2120i, e-CHEK tested by XE 2100, and 6C Cell Control tested by DxH 800 were analyzed.
*Results:* MCV of all control materials showed a tendency to increase over time. By the fifth week, most of the materials showed biases larger than one standard deviation, with some exceeding a bias of four standard deviations.
*Conclusions:* Laboratories should apply appropriate QC strategies in MCV tests by considering their individual quality and efficiency requirements.



## 1. Introduction

Stabilized blood is widely used as a multicomponent control material for the quality control (QC) of an automated hematology analyzer [1,2]. Major manufacturers of automated hematology analyzers provide commercial control materials intended for their own instruments. Most of the commercial control materials are composed of human red blood cells (RBCs), human or simulated white blood cells (WBCs), simulated platelets, and buffers including stabilizing components (the detailed constituents are slightly different between manufacturers) [3,4].

The basis of the QC process is a continued conformance of control assay values to the assigned values of the control materials [1]. It is not an easy task to find an optimal combination of preservatives that do not degrade or alter the characteristics of the blood cell components to be analyzed over storage times [3]. Through efforts made to produce stable multicomponent hematology control materials, most of the parameters of commercial control materials are maintained stable until their expiration dates. However, due to the known instability of the control materials, the mean corpuscular volume (MCV) may increase over time [1]. MCV is a measure of the average RBC volume, which allows classification of anemia as microcytic, normocytic, and macrocytic. According to the survey of American physicians, MCV was regarded as the single most useful erythrocyte index in the evaluation of anemia [5].

The increase of MCV over time makes it difficult to confirm the conformance of control assays, thus generating false positive and false negative QC results. To deal with this problem, Streck, Inc., one of the manufacturers of the control material, suggested that end-users manipulate the target mean values by adding half of the expected changes [6]. Unfortunately, there is little published information concerning the degree of bias generated by currently used commercial control materials over time. Therefore, we analyzed the QC data of three widely used control materials to investigate how instability influences the QC process of clinical laboratories. Further, since the effect of manipulating target mean has not been well described or documented, we evaluated it with 3 control materials and suggested methods to overcome the data shift of MCV in daily QC practice.

## 2. Materials and methods

### 2.1. Control materials and quality control procedures

For 16 months (from January 2012 to April 2013), QC data in a clinical laboratory in Severance Hospital, a tertiary university hospital in Seoul, Korea, were collected and reviewed. Data from lots of control materials used for more than five weeks were selected for analysis. Data that shifted due to calibration or major maintenance were excluded. In our laboratory, 6 hematology analyzers from 3 different

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manufacturers were used: 3 ADVIA 2120i (Siemens Diagnostics), 2 XE 2100 (Sysmex), and 1 Unicel DxH 800 (Beckman Coulter). Our internal QC utilized the control materials provided by the respective manufacturers. One normal level (level 1) and one high level (level 2) of TESTPoint Hematology Controls (Siemens Diagnostics) composed of human RBCs and WBCs, simulated platelets and simulated reticulocytes in a preservative medium containing neomycin and sulfate were used for QC of the ADVIA 2120i. Additionally, 3 levels of e-CHEK (Streck, Inc.) composed of human RBCs and WBCs, and simulated platelets in a preservative medium were used for QC of the XE 2100. Lastly, three levels of 6C Cell Control (Beckman Coulter, Inc.) composed of human RBCs, and simulated WBCs, platelets, and reticulocytes in a preservative medium containing sodium azide were used for QC of the DxH 800.

All the control materials were tested and stored according to the standard operating procedures of the laboratory. Following the standard of the Laboratory Accreditation Program of the Korean Society for Laboratory Medicine, control materials were tested at daily start-up and every 12 h of operation. The target mean and SD of each QC lot were calculated from the data of the first 7 days and used for establishing QC range. The expiration date of sealed and unopened control materials was about 50–70 days from the shipping date. All control materials were used prior to expiration. During the study period, daily moving averages of MCV, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were all within acceptable range. The coefficient of variation (CV) of WBC count, RBC count, hemoglobin, and platelet count obtained from each QC lots were also in the acceptable ranges.

### 2.2. Method of measuring mean corpuscular volume

ADVIA 2120i and DxH 800 directly measure MCV using the light scattering method. With the XE 2100, MCV is obtained by directly measuring hematocrit, dividing by the RBC count, and then multiplying by 10. The XE 2100 measures hematocrit by the RBC cumulative pulse-height detection method using an impedance principle.

### 2.3. Weekly average mean corpuscular volume and standard deviation index

To analyze how much MCV bias occurs over time, weekly average MCV and their standard deviation indexes (SDIs) were calculated. For each lot, the QC results of MCV were grouped on a weekly basis and were used to calculate weekly averages. The SDI was calculated by subtracting the target mean from weekly average MCV and dividing the result by SD.

### 2.4. False positive and false negative rates

False positive and false negative rates under the QC rules $1_{2s}$, $1_{3s}$, or $1_{4s}$ were estimated. Conventional QC ranges set by a target mean ± 2SD, ± 3SD, or ± 4SD were in accordance with the respective QC rules of $1_{2s}$, $1_{3s}$, or $1_{4s}$. Linear regression analyses were performed for each lot of control materials and the adjusted QC ranges were set by adding ± 2SD, ± 3SD, or ± 4SD to the intercept of the linear regression equation according to the QC rule. Adjusted QC ranges were drawn as oblique lines on Levey–Jennings charts (Fig. 1A). False positive was defined as a result inside of the adjusted QC range, but outside of the conventional QC range. False negative was defined as a result outside of the adjusted QC range, but inside of the conventional QC range. False positive or negative rates were calculated as false positive or false negative cases divided by the number of total measurements obtained from all tested lots of a control material. Cumulative false positive or false negative rates were estimated from day one for periods of 2, 3, 4, and 5 weeks.

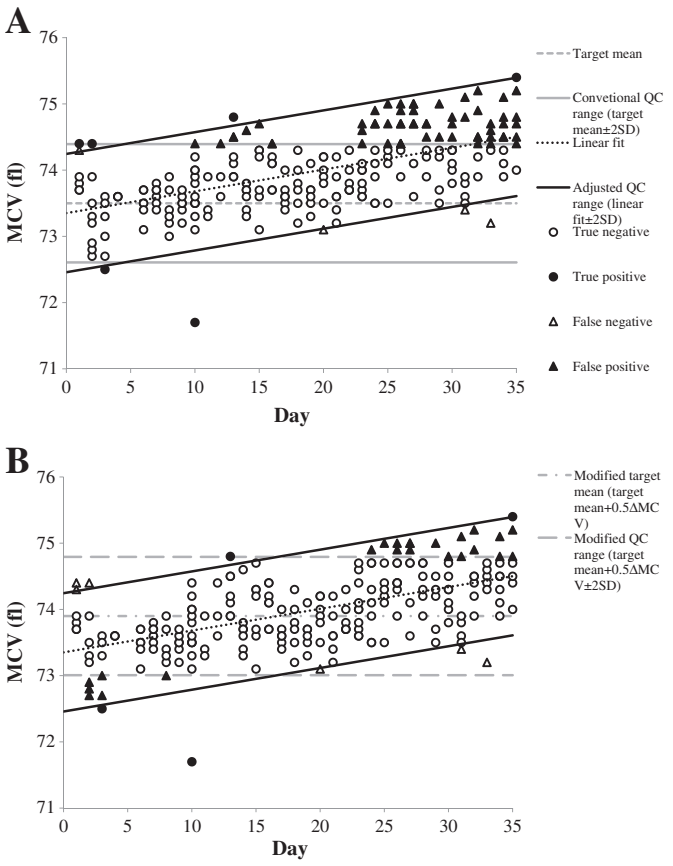


**Fig. 1.** A, An example of data from one lot of a control material plotted with conventional and adjusted QC ranges. B, Same data plotted with modified QC range and adjusted QC range.

### 2.5. Modification of target mean

Following the suggestion made by Streck, Inc., the manufacturer of e-CHEK, we modified the target mean and evaluated the false positive and false negative rates. They recommend that, if the MCV value rises a certain amount over the life of the control, it is deemed acceptable to raise the mean by half this change to accommodate the known rise [6]. Therefore, we modified the target mean by adding half of the expected changes of MCV over 5 weeks (ΔMCV). The ΔMCV was calculated as the mean MCV of the 5th week subtracted by the mean MCV of the 1st week for each lot. The median value of the ΔMCV was calculated according to the control material, and half of the value was added to the target mean of each lot. Then, we re-evaluated the false positive and false negative rates utilizing the same method described above (Fig. 1B).

### 2.6. Statistical analysis

Case-wise diagnostics were performed along with the linear regression to remove outliers in calculating target mean, modified target mean, SD, and SDI, and establishing linear regression model. Outliers were included in calculating %CV, false positive rates, and false negative rates. The linear regression analyses were performed using IBM SPSS Statistics 20.0 (SPSS, Inc.).

## 3. Results

### 3.1. Quality control data and standard deviation indexes

A total of 3642 QC results obtained from 43 lots were analyzed (Table 1). Data were obtained from five lots of each of the two levels