A model for managing Quality Control for a group of hematology instruments

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Introduction :

Monitoring Quality Control for a laboratory or network with multiple analyzers measuring the same analyte is challenging. We present a robust method based on the detection of medically important out-of-control error conditions. The purpose of the model was to ensure that results from any one of several instruments measuring the same analytes in a laboratory or a network provide comparable results and hence reduce patient risk. There has been limited literature describing how to manage QC in these very common situations. The Parvin group suggests that setting fixed QC means and SDs for multiple instruments or analytical units that perform the same assays can provide good quality control performance characteristics from the perspective of the reliability of the patient's results. We describe an approach used to build control charts with an independently assessed, fixed mean and CV common to a group of equivalent analyzers in separate geographical sites all the modules measuring the same hematology parameters.

Method

Quality control data were collected from thirty identical analytical instruments (Sysmex France, Villepinte, France, Sysmex XN-10), of seven technical sites of Biogroup laboratory located in Lyon (6 sites/20 instruments) and Paris (1 site/10 instruments). The methods studied are Spectrophotometric **Hb**, Leukocytes light scattering (**WBC**) and platelet (**Plt**) impedance. The Quality Control material was Sysmex XN-Check, Sysmex Corporation, Japan, The processing of outsourced IQC data is carried out by CaresphereTM data concentrator software

Test 1 : Confidence in the consensus mean.

Confidence in the consensus mean is assessed by calculating the confidence intervals (95% CI) from the externalization data of three batches of IQC circulating in 2022 sampled randomly,

Test 2 : The stability of the target means.

The verification of the stability of the target means, essential for the construction of common control charts with a fixed mean, was first evaluated statistically by carrying out a Student's test (α=0.05) of comparison of the means of the peer group on the first day of the release of lot 2144 (06-19-22) with those of the last day (08-12-22). Secondly, it was evaluated biologically by comparing the variation of this average with a biological reference (EFLM desirable bias).

Test 3 : The estimation of the significance of the average bias.

The estimation of the significance of the average bias of our methods about the average of the peer group was made using the test proposed by Vidali et al. This method consists in calculating the confidence interval 95 of the average of the cumulative biases of **the 15 analyzers** (5 in Lyon ; 10 in Paris) for the parameters and levels studied on batch 2256 circulating in November 2022. If the confidence interval crosses zero, the bias is not significant (α risk 0.05).

Test 4 : Random variability of methods.

The recommendations of good practice recommend the use of an analytical CV close to the real CV of the method used. However, they do not deal with a multi-site and multi-analyzer framework. T. Badrik proposes a formula to calculate the real "pooled" CV of different analyzers which can be used for the daily monitoring of the methods. We calculated the pooled CVs for **15 analyzers** (5 in Lyon ; 10 in Paris) that we compared (Fisher's test) to the weighted average of the CV_{90s} . To do this, the CV_{90s} of 15 batches of IQC circulating over 2.5 years were analyzed (physiological level). *A Shapiro-Wilk test on the CV_{90} distribution for the period analyzed showed normal recurrence.*

Test 5 : Comparison of analytical variability with the biological variation of the parameters studied :

The CV_{90s} calculated during the previous step are compared with the APS of intra-individual biological variation. The needs concerning the follow-up of the patient and the low individuality index of the hematology parameters direct towards the choice of the MAU as biological reference at the expense of the acceptable total error of the linear model (0,75CVI = MAU EFLM ; consultation 01-18-2023). The result graph was made by inserting the CV90 in the Gaussian function centered on the mean of the peer group of IQC. The expected number of unreliable patient results is calculated using the CV_{90}/MAU ratio. The result of this ratio being reported in a Student's table to deduce the probability of biologically unreliable results.

Test 6 : The IQC results were extracted from 20 analyzers in Lyon from the period from 01-27-23 to 03-23-23. The laboratory uses 3 levels of controls 3 times a day (alterned levels) i.e. one control every 128 patients. The analysis run does not start if the IQC values are more than 3SD from the target mean (SD=CV_{90} x target mean). An IQC result corresponding to a medically important error is defined by exceeding the MAU during the end or mid-run check. Thus, patient results are re-analyzed if the end-of-series control exceeds the MAU. Technical rejection rate (1-3S and R4S) and clinical rejection rate (IQC results with significant medical error) are calculated by calculating the ratio. The number of IQC excluding MAU therefore corresponds to the number of rejected series.
Finally, we noted the rate of non-compliant EQAs during the study period. This result adds proof of the accuracy of the methods on another matrix.

Results

Test 1 : The confidence interval of the mean of the peer group is inferior to the decimal of rendering for the three parameters analyzed and for each concentration level tested.

PG : peer group ; PG N : number of analyzers

Control Lot	Parameter	PG mean	PG N	IC95%
#2032(L2)_CL Apr 22	Hb g/dL	10,98	1405	0,0045
#2088(L2)_CL Jun 22		11,54	1452	0,0046
#2144(L2)_CL Aug 22		11,37	1445	0,0044
#2032(L2)_CL Apr 22	WBC G/L	6,996	1335	0,0045
#2088(L2)_CL Jun 22		6,899	1381	0,0043
#2144(L2)_CL Aug 22		6,965	1375	0,0044
#2032(L2)_CL Apr 22	PLT G/L	244,1	1335	0,2319
#2088(L2)_CL Jun 22		234,7	1381	0,2143
#2144(L2)_CL Aug 22		254	1375	0,2465

Test 2 : There is no statistically (WBC) or biologically significant (Hb, PLT) difference between the distribution of the peer group mean on the first day of the release of the analyzed batch and on the last day of its validity period.

Parameter	Mean of the peer group on the first day of release of the lot.	Mean of the peer group on the last day of release of the lot.	Experimental Student's t	Difference between the means of the 1st and the last day	Desirable bias EFLM
HB g/dl	11,35	11,37	4,4	0,18%	1,60%
WBC G/L	6,968	6,965	0,6	0,04%	4,90%
Plt G/L	252,1	253,9	7,2	0,70%	5%

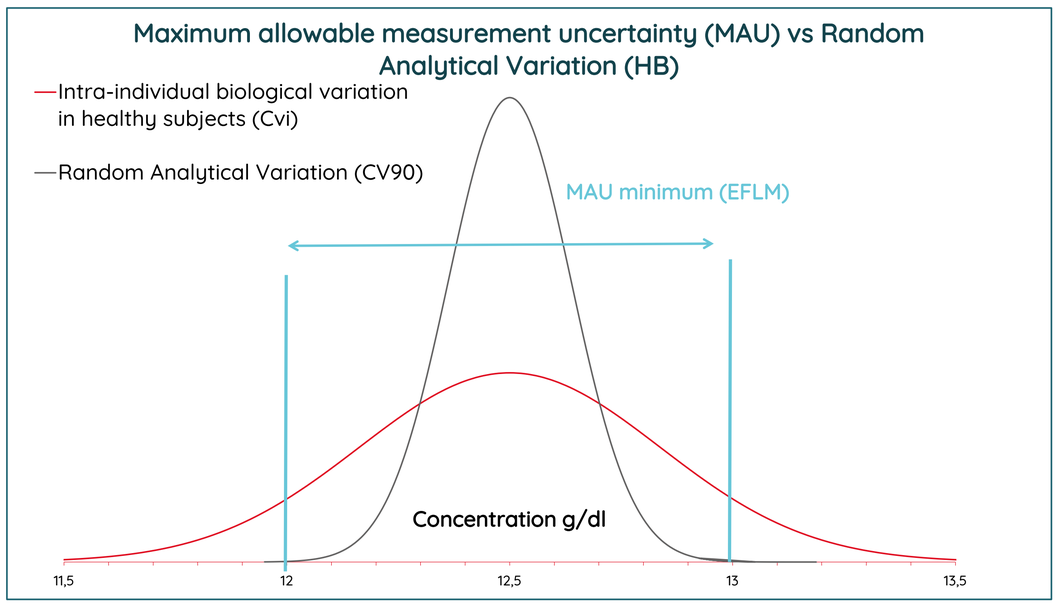
Test 3 : The 95% CIs of the average bias of the 15 modules for the physiological levels of IQC (L2) for HB, WC and Plt cross 0. The methods of the laboratories studied do not include any real significant bias.

	HB	WBC	Pl
IC95 of the average bias of the analyzers studied	-0,7 to 0,1	-0,5 to 0,67	-0,23 to 1,07

Test 4 : The actual pooled CVs of laboratories are comparable to the CV90 for hemoglobin and leukocytes. The CV90 of the platelets is significantly higher than the pooled CV of the beta-testing laboratories. Nevertheless, this pooled CV (1.9%) is insignificant with regard to the CV_I of this parameter (7.6%, EFLM). The CV90s can therefore be used to build common control cards for all the analyzers of the same range.

Bacth #2256 (11-2022 ; N2)	Weighted average of the CV90s	"pooled" CV	Ratio
HB	1,1	1,0	1,1
WBC	2	1,6	1,2
Plt	3,3	1,9	1,8

Test 5 : The CV_{90} are inferior to the APS specifications. The expected rate of unreliable results when estimating the performance of methods with the CV_{90} is less than 0.1% for the three parameters studied.



Test 6 : The technical rejection rate (1-3s/R4S) for **HB**, **WBC** and **Plt** is respectively 0,14% (3/2,185) ,0,18% (4/2,184), 0,27% (6/2,183) . The clinical rejection rate is 0 : none of the IQC presented a result outside MAU. We didn't observe any non-compliant EQA result during the analyzed period.

Discussion / Conclusion

The overall strategy of IQC is to ensure that the laboratory produces results within specifications that are fit for clinical purposes. The additional requirement is that results from any instrument in the laboratory must be comparable.

The presented model uses the same statistical rejection rules but also adds a clinically fit-for-purpose assessment rule to reduce blocking of patient results or unjustified maintenance.

A main question about monitoring IQC is "what is a 'significant change'? ". In the model presented in this poster, the statistical approach detects a trend or shift in the method. Then, the detected bias is assessed against clinical criteria related to biological variation (CV_I).

This process allows the harmonization of quality control procedures, specifically answering the question "what is an "acceptable bias"?. This is a critical component of producing consistent results for a patient no matter where and when their sample is analyzed. The availability of accessible peer group data allows the implementation of new lots of IQC material to be undertaken faster, more easily and with greater confidence. This also reduces the amount of IQC material needed to establish the reference target average and improves the efficiency of setting up a new batch of control.

The consumption of IQC material is a significant environmental and financial waste. Implementing this approach has been quick and easy, as the CV_{90} and peer group average data are readily accessible. These peer group data are implemented in the middleware which ensures a daily update. Monitoring for bias is simplified using Levey-Jennings charts which also allows the continuous comparability of all analytical modules across all sites.

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