TECHNICAL REPORT

Remote Calibration Verification, Cycle-based Maintenance Schedules and Quality Control Sigmas in the United States Market

Jennifer Le BREUX[*1], Emily CEDERLAND[*2], Steve POSTIMA[*3] and Ian GILES[*1]

[*1] Scientific Affairs, Sysmex America Inc., One Nelson C White Parkway, Mundelein IL 60060, USA
[*2] Assay Laboratory, Sysmex America Inc., One Nelson C White Parkway, Mundelein IL 60060, USA
[*3] Service Department, Sysmex America Inc., One Nelson C White Parkway, Mundelein IL 60060,USA

SUMMARY

The statistical approaches advocated by James Westgard are applied and valued internationally. The use of clinical goals which are analyte specific is an approach which is highly appropriate for defining and judging measurement performance in biological systems. Analyte specific, and concentration specific performance at clinical decision points can now be reliably and appropriately designed and judged.
Examples of how simple Sigma calculations, OPSpecs Charts and Westgard QC Rules can be applied are described. Specific information relating to the mathematical approaches and tools is available on the website at: www.westgard.com, and is beyond the scope of this article.

APPLICATIONS

The incorporation of a clinical quality goal as a component in Sigma metric calculations is a significant step forward in any instrument design specification development. In collaboration with experts on biological variation, the concepts proposed by Jim Westgard bring clarity and potential standardization to performance determination and enhancement. While the concepts were developed for, and work best in Clinical Chemistry and Immunology, the stability and purity challenges faced in Hematology remain, and through the use of Westgard applications, can be managed appropriately.
The mathematical approaches proposed by Westgard can be applied at multiple levels within our entire quality control process (multiple data sets from multiple instruments), and can provide reliable and appropriate insight into the relevance of certain processes and existing performance on instruments in any setting. For example, in a Research and Development environment, in our Assay value assignment lab, on a single instrument, a single institution, or an entire instrument installed base. Information retrieved can highlight and differentiate probable origins of deficient performance, and allow focused efforts to reduce components of error within complex systems. The mathematical approaches proposed by Westgard can be applied to error budgeting in instrument design specifications. Traditionally, specification decisions relating to new instruments have been based almost exclusively on competitive analysis, and final decisions have been made by individuals or consensus, without the luxury of being able to design instruments according to clinically relevant performance goals.
By applying simple Sigma calculations to data sets from multiple components of the laboratory / manufacturing system, assessments and comparisons can be made that enable realistic change relative to clinical diagnostic performance requirements, and varying regulatory restrictions.

SINGLE INSTRUMENT PERFORMANCE

The use of OPSpecs Charts provides clearly visible evidence of test performance requirements, and QC monitoring needs relative to the clinical performance goals at a specific analyte concentration, and clinical decision threshold.

The example shown below is an OPSpecs Chart of performance on a single Sysmex XE-2100 instrument (***Fig.1***).

Table 1 is a summary of the recommended QC rules and the resulting reductions in false rejection from common control practices.

A detailed explanation of individual parameter performance is available on the Westgard website at: http://www.westgard.com/qcapp41.htm

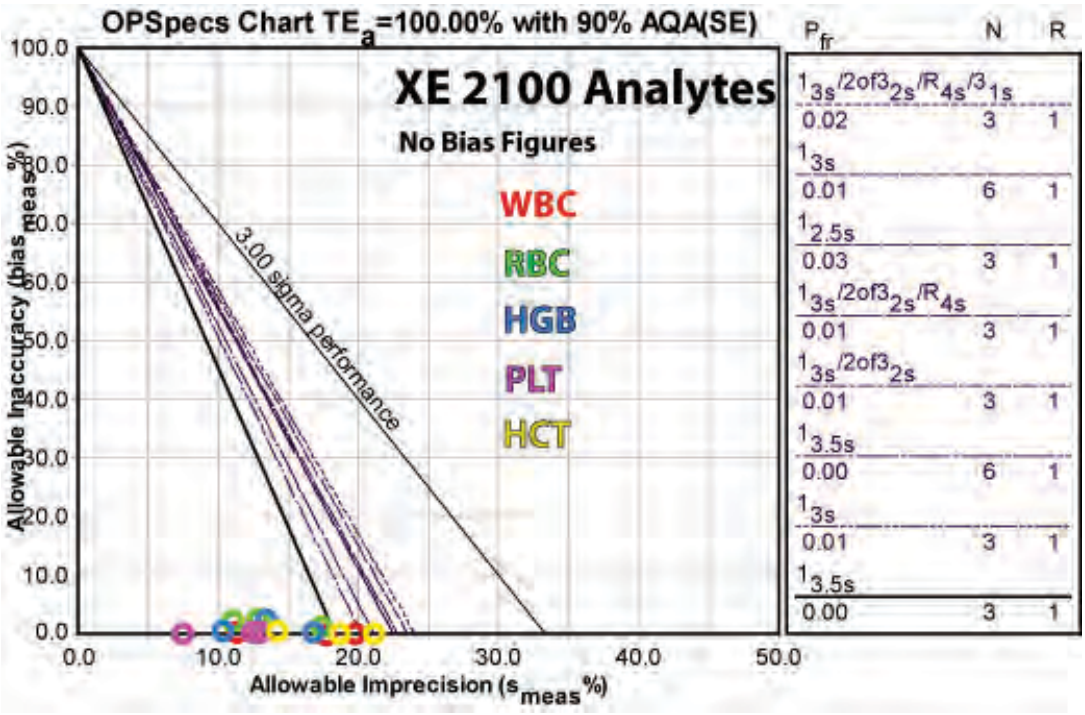

Fig. 1 *OPSpecs chart of performance on a single Sysmex XE-2100 instrument.*

Table 1 *Summary of the recommended QC rules and the resulting reductions in false rejection*

Analyte	QC Rule Implemented	False Rejection (P_{fr})	Reduction from 1_{2s} rule N = 3 P_{fr} (0.14)	Reduction from full "Westgard Rules" N = 3 (P_{fr} = 0.02)
HCT	1_{3s} with N = 3	0.01	93% reduction in false rejections	50% reduction in false rejections
HGB	$1_{3.5s}$ with N = 3	essentially zero	nearly 100% reduction	nearly 100% reduction
RBC	$1_{3.5s}$ with N = 3	essentially zero	nearly 100% reduction	nearly 100% reduction
WBC	$1_{3.5s}$ with N = 3	essentially zero	nearly 100% reduction	nearly 100% reduction
PLT	$1_{3.5s}$ with N = 3	essentially zero	nearly 100% reduction	nearly 100% reduction

QUALITY CONTROL SYSTEMS AND MATERIALS

Westgard Rules are widely applied, and are particularly useful in that they ***reduce the incidence of false rejection***, and bring a graduated approach to requirements for controlling tests. In simple terms, the poorer the capability of the test, the bigger the requirement for multiple QC repeats at multiple analyte concentrations.

It must be recognized that what we are measuring in QC data is a surrogate system, developed in order to overcome the stability challenges associated with transportation of whole human blood samples. If there was a way to maintain stability of human blood for extended timeframes, there would in fact be no need for quality control products.

Logistical constraints and climate play a major role in quality control and sample stability, and the challenges are greater in larger countries, underdeveloped countries, and countries with extremes in temperature variation.

In Hematology, stabilized live cells invariably make up the bulk of the components in the quality materials. Typically these components are of non-human origin, and some synthetic materials are used. There is no absolute requirement to use live cells, but current synthetic surrogates are expensive and difficult to apply across the spectrum of cell types.

In Clinical Chemistry there are primary and secondary standards available which are separated by virtue of their purity and link to a traceable standard. In Hematology, this is less evident. Traceable standards being human blood, but the differences in "purity" between calibrators and QC materials is small or non-existent. Proficiency testing is traditionally done through the use of the same quality control materials as those used to routinely control the instruments.

In all Hematological cell counting, stability of products and samples is the source of the bulk of the variability. This is due to osmotic, temperature and metabolic changes within transport vials that impact cell morphology. Pre-analytical variability should be the focus of troubleshooting, and the secret often lies in the logistical support systems. Delivery times to labs, and temperature control are central to good quality control monitoring. Pre-analytical factors associated with temperature and sample mixing are important considerations, and training of cross-functional staff members can be used to address some of these components.

The service offered by instrument manufacturers can therefore be seen as twofold; 1) addressing the performance of instrument and reagent systems on patient blood in laboratories geographically associated with patients they serve; and 2) monitoring a surrogate product (that does not perfectly mimic changes in human blood, but is our best attempt at that).

This dissociation is recognized by advocates of monitoring moving averages in patient populations. It also opens the door for potential development of alternative approaches to monitoring instrument performance going forward. In the meantime it is important to recognize that the system we employ for monitoring performance is often more of a challenge than testing patient samples, and is hampered by stability of blood and quality testing materials. There is a good chance that instrument performance on human blood collected nearby without delay, is better than that from data collected on multiple instruments geographically scattered throughout the world. The logistical, temperature, training conditions and variability in pre-analytical steps of the surrogate system are likely more difficult to control, than conditions on an individual instrument which receives freshly sampled local human blood.

It is for these reasons, that reducing false rejection of QC results makes sense from an efficiency perspective.

ASSESSING PROCESSES WITHIN THE QUALITY SYSTEM

Looking at data sets in each sector of the quality process is a useful exercise in order to critically assess existing practice, and identify opportunities for performance enhancement if clinically required, and to justify existing practices if clinical performance goals are already being achieved at clinically relevant analyte concentrations.

Steps in the assay assignment process can be broken down and investigated in isolation, and contributions from each phase to overall performance can be judged. If certain procedures are not achieving good Sigma values, those procedures can become the focus of enhancement efforts.

By looking at Sigma values of the entire instrument installed base, and by identifying uncompetitive components of the quality process, specific steps can be introduced in order to refine the existing approach. By identifying sources of bias and imprecision within the peer group, and by understanding the impact that they have on achieving performance targets for clinical decision making, improvement efforts can become far more focused and sensible. In addition, if no improvement is required, existing performance can be robustly defended.

An example of how these approaches have been applied at Sysmex is described below. During 2005-2006, an assessment of our existing installed base was undertaken in order to look for potential opportunities to refine our existing approach to calibrator assay value assignment and our entire quality control process.

An initial assessment of the peer group data suggested that the performance requirements within the assay assignment component were adequate, but that performance in the field offered an opportunity to improve. This was not unexpected since the contributions to variability and bias are much more likely to occur outside a controlled environment with optimal training, good instrument condition and maintenance, and a single analyzer with dedicated staff.

During the assay assignment process, calibrators and control materials are fresh and vigilance is high. Since the biggest contribution to bias and imprecision in the

field is likely to be related to product instability, temperature control and logistical challenges, variability of training, multiple instruments in varying condition etc., focus was placed on variability sources downstream of the value assignment process.

REMOTE CALIBRATION VERIFICATION

CLIA regulations currently specify the requirement to perform calibration verification on a 6 monthly basis. Existing practice was to recalibrate all instruments on a 6 monthly basis, as part of the routine service maintenance call. This approach was modified in order to introduce a "cycle-based" service maintenance schedule, whereby the routine maintenance of instruments would be performed according to instrument usage (number of tests done), as opposed to routine 6 monthly maintenance intervention. This enhancement introduced efficiencies not only in terms of service intervention, but also allowed the justification of remote "calibration verification" as opposed to routine 6 monthly calibration. Remote calibration has been made possible through the use of the Sysmex E verify process, and the SNCS networking system.
The impact of these changes can be seen in the data tables presented below. The data shows Sigma Values for the 5 principle parameters with existing clinical performance goals as specified in CLIA'88 goals for proficiency testing. Calculation of Sigma values in this instance were done by using the formula: σ = (Clinical Performance Goal - Group Bias) / Group CV.

Note:
e-Verify is a remote calibration verification program designed to support our customers in meeting the CLIA, CAP and state requirements for calibration verification of every 6 months.
Cycle-based Maintenance is a program designed to align the preventive maintenance (PM) activity to be based on instrument cycles rather than time intervals.

CONCLUSION

Adoption and application of approaches proposed by James Westgard provides highly appropriate insight on multiple levels of assay design and judgment. These techniques can be applied to all aspects of instrument or assay development and monitoring; from determining / justifying developmental performance specifications, through applications in monitoring instrument installed-base performance.
We show by example how these tools have been used to identify opportunities for process enhancement, by appropriately judging existing processes, measuring and understanding performance on single instruments in well controlled environments and on multiple instruments in diverse environments.
Once legitimate targets are identified in this way, appropriate opportunities can be identified and implemented, and the impact of the change can be appropriately quantified, with a link to analyte - specific performance goals.
Evidence of improvement is clearly demonstrated by comparing the 2005-2006 data with data from 2008-2009 in ***Table 2, 3A-3E***.

Note:
The Formulae used in ***Table 2, 3A-3E*** are summarized as the following.
* Assay value is the target value of QC material as determined prior to distribution.
* Group Mean is the mean of QC values submitted via our Insight program for monitoring installed base QC results.
* Group CV is the calculated CV for the data submitted via our Insight program for monitoring installed base QC results.
* Group bias is the absolute difference between the Group Mean and the assigned Assay Value for that parameter.
* Group Sigma is calculated by incorporating the clinical performance goal (using the CLIA '88 values used for Proficiency Testing of the 5 key parameters, for example 6% for HGB).
  Group Sigma = (Clinical performance goal - Group Bias) / Group CV

Table 2 *Comparison of Group Sigma before and after applying Sigma calculations*

Timeframe	RBC Grp Sigma (CLIA)	HGB Grp Sigma (CLIA)	HCT Grp Sigma (CLIA)	PLT Grp Sigma (CLIA)	WBC Grp Sigma (CLIA)
2005-2006	4.69	5.62	3.65	6.71	5.06
2008-2009	7.37	9.00	4.57	9.35	6.50

Table 3A *Statistics summary of RBC*

XE-2100-NORMAL L2	RBC Assay	RBC Grp Mean	RBC Grp Bias	RBC Grp Sigma (CLIA)	RBC Grp CV	RBC Grp SD
Lot 8064 3/5/08 - 5/26/08	4.30	4.30	0.00	7.50	0.80	0.04
Lot 8120 4/30/08 - 7/21/08	4.31	4.32	0.01	6.66	0.90	0.04
Lot 8176 6/25/08 - 9/15/08	4.33	4.33	0.00	7.50	0.80	0.03
Lot 8233 09/30/08 - 11/10/08	4.37	4.37	0.00	7.50	0.80	0.03
Lot 8288 10/15/08 - 1/5/09	4.32	4.34	0.02	7.48	0.80	0.03
Lot 8344 12/10/08 - 3/2/09	4.31	4.34	0.03	7.47	0.80	0.04
Lot 9034 2/4/09 - 3/16/09	4.32	4.35	0.03	7.46	0.80	0.04
MEAN	4.32	4.34	0.01	7.37	0.81	0.04
MAX	4.30	4.30	0.00	6.66	0.80	0.03
MIN	4.37	4.37	0.03	7.50	0.90	0.04
CV	0.53	0.54	98.64	4.26	4.64	14.97
SD	0.02	0.02	0.01	0.31	0.04	0.01

XE-2100-NORMAL L2	RBC Assay	RBC Grp Mean	RBC Grp Bias	RBC Grp Sigma (CLIA)	RBC Grp CV	RBC Grp SD
Lot 5165 6/15/05 - 8/18/05	5.30	5.21	0.09	4.22	1.40	0.07
Lot 5221 8/10/05 - 10/14/05	5.33	5.24	0.09	4.92	1.20	0.06
Lot 5277 10/5/05 - 12/9/05	5.30	5.21	0.09	4.93	1.20	0.06
Lot 5334 11/30/05 - 2/3/06	5.23	5.14	0.08	4.55	1.30	0.07
Lot 6024 1/25/06 - 3/31/06	5.31	5.24	0.07	4.94	1.20	0.06
Lot 6080 3/22/06 - 5/26/06	5.13	5.07	0.06	4.57	1.30	0.07
MEAN	5.27	5.19	0.08	4.69	1.27	0.07
MAX	5.33	5.24	0.09	4.94	1.40	0.07
MIN	5.13	5.07	0.06	4.22	1.20	0.06
CV	1.42	1.28	17.11	6.26	6.45	6.05
SD	0.08	0.07	0.01	0.29	0.08	0.00

Table 3B *Statistics summary of HGB*

XE-2100-NORMAL L2	HGB Assay	HGB Grp Mean	HGB Grp Bias	HGB Grp Sigma (CLIA)	HGB Grp CV	HGB Grp SD
Lot 8064 3/5/08 - 5/26/08	11.90	11.99	0.09	8.64	0.80	0.09
Lot 8120 4/30/08 - 7/21/08	12.50	12.54	0.04	8.70	0.80	0.10
Lot 8176 6/25/08 - 9/15/08	12.20	12.16	0.04	9.94	0.70	0.10
Lot 8233 09/30/08 - 11/10/08	12.40	12.44	0.04	8.70	0.80	0.10
Lot 8288 10/15/08 - 1/5/09	12.50	12.62	0.12	8.60	0.80	0.20
Lot 8344 12/10/08 - 3/2/09	12.00	12.13	0.13	8.59	0.80	0.20
Lot 9034 2/4/09 - 3/16/09	12.40	12.48	0.13	9.81	0.70	0.19
MEAN	12.27	12.34	0.08	9.00	0.77	0.14
MAX	11.90	11.99	0.04	8.59	0.70	0.09
MIN	12.50	12.62	0.13	9.94	0.80	0.20
CV	1.98	1.95	51.65	6.72	6.33	37.84
SD	0.24	0.24	0.04	0.60	0.05	0.05

XE-2100-NORMAL L2	HGB Assay	HGB Grp Mean	HGB Grp Bias	HGB Grp Sigma (CLIA)	HGB Grp CV	HGB Grp SD
Lot 5165 6/15/05 - 8/18/05	16.95	16.71	0.24	5.63	1.20	0.20
Lot 5221 8/10/05 - 10/14/05	16.84	16.58	0.26	5.62	1.20	0.20
Lot 5277 10/5/05 - 12/9/05	16.96	16.68	0.28	5.60	1.20	0.20
Lot 5334 11/30/05 - 2/3/06	16.36	16.60	0.24	5.63	1.20	0.20
Lot 6024 1/25/06 - 3/31/06	16.71	16.45	0.26	5.62	1.20	0.20
Lot 6080 3/22/06 - 5/26/06	16.25	15.98	0.27	5.61	1.20	0.19
MEAN	16.68	16.50	0.26	5.62	1.20	0.20
MAX	16.96	16.71	0.28	5.63	1.20	0.20
MIN	16.25	15.98	0.24	5.60	1.20	0.19
CV	1.83	1.64	6.20	0.24	0.00	1.64
SD	0.30	0.27	0.02	0.01	0.00	0.00

Table 3C *Statistics summary of HCT*

XE-2100-NORMAL L2	HCT Assay	HCT Grp Mean	HCT Grp Bias	HCT Grp Sigma (CLIA)	HCT Grp CV	HCT Grp SD
Lot 8064 3/5/08 - 5/26/08	34.80	35.02	0.22	4.13	1.40	0.50
Lot 8120 4/30/08 - 7/21/08	36.50	36.63	0.13	4.52	1.30	0.47
Lot 8176 6/25/08 - 9/15/08	35.40	35.45	0.05	4.96	1.20	0.44
Lot 8233 09/30/08 - 11/10/08	36.20	36.53	0.33	4.73	1.20	0.46
Lot 8288 10/15/08 - 1/5/09	36.40	36.57	0.17	4.48	1.30	0.47
Lot 8344 12/10/08 - 3/2/09	35.30	35.40	0.10	4.54	1.30	0.47
Lot 9034 2/4/09 - 3/16/09	37.10	36.70	0.40	4.67	1.20	0.44
MEAN	35.96	36.04	0.20	4.57	1.27	0.46
MAX	34.80	35.02	0.05	4.13	1.20	0.44
MIN	37.10	36.70	0.40	4.96	1.40	0.50
CV	2.25	2.00	63.11	5.58	5.95	4.46
SD	0.81	0.72	0.13	0.26	0.08	0.02

XE-2100-NORMAL L2	HCT Assay	HCT Grp Mean	HCT Grp Bias	HCT Grp Sigma (CLIA)	HCT Grp CV	HCT Grp SD
Lot 5165 6/15/05 - 8/18/05	46.73	46.84	0.11	3.68	1.60	0.75
Lot 5221 8/10/05 - 10/14/05	46.80	46.74	0.06	3.71	1.60	0.75
Lot 5277 10/5/05 - 12/9/05	46.87	46.72	0.15	3.66	1.60	0.75
Lot 5334 11/30/05 - 2/3/06	46.41	46.22	0.19	3.63	1.60	0.74
Lot 6024 1/25/06 - 3/31/06	46.45	46.35	0.10	3.69	1.60	0.74
Lot 6080 3/22/06 - 5/26/06	45.12	45.12	0.00	3.53	1.70	0.77
MEAN	46.40	46.33	0.10	3.65	1.62	0.75
MAX	46.87	46.84	0.19	3.71	1.70	0.77
MIN	45.12	45.12	0.00	3.53	1.60	0.74
CV	1.41	1.38	65.66	1.78	2.53	1.19
SD	0.65	0.64	0.07	0.07	0.04	0.01

Table 3D *Statistics summary of PLT*

XE-2100-NORMAL L2	PLT Assay	PLT Grp Mean	PLT Grp Bias	PLT Grp Sigma (CLIA)	PLT Grp CV	PLT Grp SD
Lot 8064 3/5/08 - 5/26/08	214.00	217.00	3.00	9.17	2.40	5.18
Lot 8120 4/30/08 - 7/21/08	217.00	221.00	4.00	8.40	2.50	5.59
Lot 8176 6/25/08 - 9/15/08	212.00	212.00	0.00	10.00	2.50	5.25
Lot 8233 09/30/08 - 11/10/08	213.00	214.00	1.00	9.60	2.50	5.46
Lot 8288 10/15/08 - 1/5/09	214.00	216.00	2.00	9.58	2.40	5.27
Lot 8344 12/10/08 - 3/2/09	224.00	226.00	2.00	9.58	2.40	5.50
Lot 9034 2/4/09 - 3/16/09	221.00	225.00	4.00	9.13	2.30	5.09
MEAN	216.43	218.71	2.29	9.35	2.43	5.33
MAX	212.00	212.00	0.00	8.40	2.30	5.09
MIN	224.00	226.00	4.00	10.00	2.50	5.59
CV	2.08	2.47	65.45	5.48	3.11	3.45
SD	4.50	5.41	1.50	0.51	0.08	0.18

XE-2100-NORMAL L2	PLT Assay	PLT Grp Mean	PLT Grp Bias	PLT Grp Sigma (CLIA)	PLT Grp CV	PLT Grp SD
Lot 5165 6/15/05 - 8/18/05	211.00	219.00	8.00	6.07	2.80	6.13
Lot 5221 8/10/05 - 10/14/05	210.00	218.00	8.00	6.07	2.80	6.10
Lot 5277 10/5/05 - 12/9/05	213.00	218.00	5.00	7.14	2.80	6.10
Lot 5334 11/30/05 - 2/3/06	213.00	217.00	4.00	7.50	2.80	6.08
Lot 6024 1/25/06 - 3/31/06	213.00	217.00	4.00	7.24	2.90	6.29
Lot 6080 3/22/06 - 5/26/06	210.00	217.00	7.00	6.21	2.90	6.29
MEAN	211.67	217.67	6.00	6.71	2.83	6.17
MAX	213.00	219.00	8.00	7.50	2.90	6.29
MIN	210.00	217.00	4.00	6.07	2.80	6.08
CV	0.71	0.38	31.62	9.81	1.82	1.61
SD	1.51	0.82	1.90	0.66	0.05	0.10

Table 3E *Statistics summary of WBC*

XE-2100-NORMAL L2	WBC Assay	WBC Grp Mean	WBC Grp Bias	WBC Grp Sigma (CLIA)	WBC Grp CV	WBC Grp SD
Lot 8064 3/5/08 - 5/26/08	7.11	7.00	0.11	6.48	2.30	0.16
Lot 8120 4/30/08 - 7/21/08	6.96	6.92	0.04	6.51	2.30	0.16
Lot 8176 6/25/08 - 9/15/08	6.95	6.98	0.03	6.51	2.30	0.16
Lot 8233 09/30/08 - 11/10/08	7.15	7.05	0.10	6.77	2.20	0.16
Lot 8288 10/15/08 - 1/5/09	6.93	6.90	0.03	6.51	2.30	0.16
Lot 8344 12/10/08 - 3/2/09	7.09	7.02	0.07	6.49	2.30	0.16
Lot 9034 2/4/09 - 3/16/09	6.83	6.85	0.01	6.24	2.40	0.16
MEAN	7.00	6.96	0.06	6.50	2.30	0.16
MAX	6.83	6.85	0.01	6.24	2.20	0.16
MIN	7.15	7.05	0.11	6.77	2.40	0.16
CV	1.65	1.05	67.14	2.35	2.51	0.00
SD	0.12	0.07	0.04	0.15	0.06	0.00

XE-2100-NORMAL L2	WBC Assay	WBC Grp Mean	WBC Grp Bias	WBC Grp Sigma (CLIA)	WBC Grp CV	WBC Grp SD
Lot 5165 6/15/05 - 8/18/05	6.74	6.22	0.52	4.53	3.20	0.20
Lot 5221 8/10/05 - 10/14/05	6.70	6.67	0.03	4.99	3.00	0.20
Lot 5277 10/5/05 - 12/9/05	6.67	6.64	0.03	4.99	3.00	0.20
Lot 5334 11/30/05 - 2/3/06	6.81	6.75	0.06	5.15	2.90	0.20
Lot 6024 1/25/06 - 3/31/06	6.80	6.75	0.04	5.34	2.80	0.19
Lot 6080 3/22/06 - 5/26/06	6.47	6.46	0.01	5.35	2.80	0.18
MEAN	6.70	6.58	0.11	5.06	2.95	0.19
MAX	6.81	6.75	0.52	5.35	3.20	0.20
MIN	6.47	6.22	0.01	4.53	2.80	0.18
CV	1.85	3.14	172.95	6.05	5.14	3.93
SD	0.12	0.21	0.20	0.31	0.15	0.01