How to Successfully Migrate Assays following the 2009 FDA Draft Guidance Policy

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FDA Draft Migration Policy

- The FDA Draft Migration Policy was published on January 5, 2009
- Issued jointly by CDRH OIVD and CBER
- It is a 27 page document with two appendices
- Appendix 1 – CBER Migration Studies for Blood Donor Screening Assays
- Appendix II – Statistical Notes

➢ AdvaMed formed a working subgroup to supply comments on the draft guidance, 13 pages of comments submitted on April 6, 2009

FDA Draft Migration Policy-FDA Presentations in 2009 and 2010

- Draft Guidance: Assay Migration Studies for *In Vitro* Diagnostic Devices: Sally A. Hojvat PhD, OIVD/CDRH and Marina V. Kondratovich, PhD, OSB/CDRH – Presentation at the AMDM 36th Annual Meeting April 23, 2009

- Draft Guidance: Assay Migration Studies for *In Vitro* Diagnostic Devices: Sally A. Hojvat PhD, Stefanie Akselrod MD and Marina V. Kondratovich, PhD – Presentation at the FDA/Industry Roundtable Meeting January 13, 2010

Introduction to Migration Studies

1. Introduction

- Draft guidance represents a least burdensome regulatory approach to gain FDA approval of a Class III or certain licensed in vitro diagnostic devices where a previously approved or licensed test is “migrating or transitioning” to another system that has not been previously approved or licensed
- “Old System” refers to the approved/licensed system (assay, instrument and software)
- “New System” refers to the un-approved/un-licensed system (assay, system and software)
- Contact FDA CDRH OIR (OIVD) for devices they regulate, submit a pre-Sub submission or meeting request
- Contact FDA CBER DETTD for devices they regulate, submit a pre-Sub request (usually a Type B meeting request)

Background and Scope

2. Background and Scope

- FDA believes this draft guidance provides a pathway for manufacturers to transfer a previously approved or licensed assay with full clinical data from an Old System to a New System (PMA and BLA assays and cleared assays where there may be a concern)
- The migration studies approach is related to the Replacement Reagent and Instrument Family Policy that FDA uses for Many Class I and Class II assays
- Possible scenarios include manual to semi-automated or automated platforms, semi-automated to automated or one automated system to another
- Ideally suited for test systems where assay output is a numerical result or expressed in signal to cutoff (S/CO)

FDA Draft Migration Policy

- Critical Considerations for Determining if Migration Studies May Apply to a Particular Device

- The Intended Use and Indications for Use should be unchanged except for inclusion of the New System
- Reagent and assay parameters (e.g. cutoff, incubation time and temperatures) should be unchanged except for very minor changes
- Assay and system technologies should remain unchanged

Other Studies

- Other Studies – the following studies may be needed, if not performed on the “Old System” they have to be performed on the “New System”
  - Carry-over and cross-contamination studies
  - Matrix equivalency and recovery studies
  - Interfering substances studies
  - On-board reagent/calibrator and sample stability studies
  - Cross-reactivity studies
  - Hook Effect studies
  - Verification of kit control materials and calibrators

Qualitative Assays Migration Studies

- MIGRATION STUDIES FOR QUALITATIVE ASSAY
  1. Analytical Studies for Qualitative Assays-
     - Performance at low analyte levels
     - Precision study
     - Reproducibility study
  2. Comparison Studies for Qualitative Assays
     - Comparison panels
     - Testing venue- minimum is one site “Old System”, 3 sites for “New System”
  3. Statistical Analysis of Data
     - Within-laboratory precision
     - Reproducibility
     - Comparison Panels
  4. Acceptance Criteria for Qualitative Assay Migration Studies
     - Systematic difference in s/co should not be statistically and/or clinically significant
     - Ratio of SD in the precision and reproducibility studies should be either statistically and/or clinically not significant
     - In testing comparison panels, the lower limits of the two sided 95% CI for both positive and negative agreement between “Old” and “New” Systems should be > 90%. Discordant results can only occur with samples close to the cutoff and not with moderate or high positive or moderate and low negative samples.

Quantitative Assay Migration Studies

- MIGRATION STUDIES FOR QUANTITATIVE ASSAY
  1. Analytical Studies for Quantitative Assays
  2. Comparison Studies for Quantitative Assays
  3. Statistical Analysis of Data
  4. Acceptance Criteria for Quantitative Assay Migration Studies

Statistical Analysis Requirements

- Percent Agreement Tables
- Histograms
- Descriptive Statistics Table
- Scatter-Plots/ Deming Regression Analysis
- Mean Differences Table
- Dilutional Panel Comparisons
- Reproducibility Comparisons
- Precision of New Instrument
- Determination of Clinical Significance for Sensitivity
- Determination of Clinical Significance for Specificity

Molecular Assays Migration Studies

➢ Molecular Assays

- Specific criteria that are unique to nucleic acid tests (NAT) and present additional specific concerns over serological and antigen assays
- Panels with a rise in viral titer over time from serial bleeds similar to sero-conversion panels should be tested
- Carryover studies should be performed for all NAT migration studies
- Sample Stability due to delicate nature of DNA and RNA
- Sample Processing is critical and needs to be evaluated
- Validation of control material and calibrators
- “For multi-analyte molecular assays – please contact FDA”

Not applicable for Migration Studies

- Migration Studies would not be applicable to the following
- Systems intended for over-the-counter use
- Systems intended for prescription home use
- Devices intended for point of care (POC) use
- Devices that do not met the Critical Considerations criteria (e.g. change in intended use, significant change to assay cutoff, change in technologies, etc)

Appendix I and II

- APPENDIX I – MIGRATION STUDIES FOR BLOOD DONOR SCREENING ASSAYS
  1. Introduction
  2. Comparison Panels
  3. Acceptance Criteria
  4. Interfering Substances and Conditions

- APPENDIX II – STATISTICAL NOTES

FDA User Fees for Migration Studies

- FDA User Fee Rates for Devices: **2013**

- Migration Studies for a PMA diagnostic device are submitted as PMA 180-day Supplements – **$37,200 USD** ($9,300)

- Migration Studies for a FDA licensed blood screening assay are submitted at BLA Supplements – No User Fee at the current time

Glossary of Terms

- Glossary of terms
- C_5 (high neg): an amount that tests positive 5% of time
- C_{95} (low pos): an amount that tests positive 95% of time
- Carry-over: amount of analyte carried from one sample reaction to the next
- Cutoff value (CO): test threshold between neg and pos
- Medical decision level or point: critical level for assay
- Moderate positive sample: close to CO but 100% agreement
- Spiked sample: clinical sample with additional analyte
- Systemic difference: mean on “New” System value minus mean value on “Old System value

Regulatory Outcomes

- Should the acceptance criteria be met, the sponsor can claim that the “New System” does not compromise the results as compared to the “Old System”

- Not appropriate to “claim improved performance”

- Not appropriate to “claim clinical performance claims for the “New System” based on migration studies

➢ If the acceptance criteria are not met and based on FDA’s best judgment, the “aberrant performance” could affect clinical management – you will be asked to perform a complete clinical study on the “New System”

Successful Migration Studies at Bio-Rad

- Manual testing migrated to EVOLIS Automated instrument for diagnostic testing
  - MONOLISA Anti-HBs EIA (quant claim) – PMA supplement
  - MONOLISA Anti-HBc Total EIA – PMA supplement
  - MONOLISA Anti-HBc IgM EIA – PMA supplement
  - GS HIV *PLUS O* EIA – BLA supplement
- Manual testing migrated to EVOLIS Automated instrument for blood bank use
  - GS HIV-2 EIA – BLA supplement (under FDA review)
- Manual testing migrated to Elite Automated instrument for diagnostic testing
  - GS HIV Combo Ag/Ab EIA – PMA supplement
- Manual testing migrated to Ortho Summit Automated instrument for blood screening
  - GS HIV *PLUS O* EIA – BLA supplement
  - GS HBsAg EIA 3.0 – BLA supplement

Bio-Rad GS HIV-1/HIV-2 *PLUS O* EIA – 3rd Generation assay

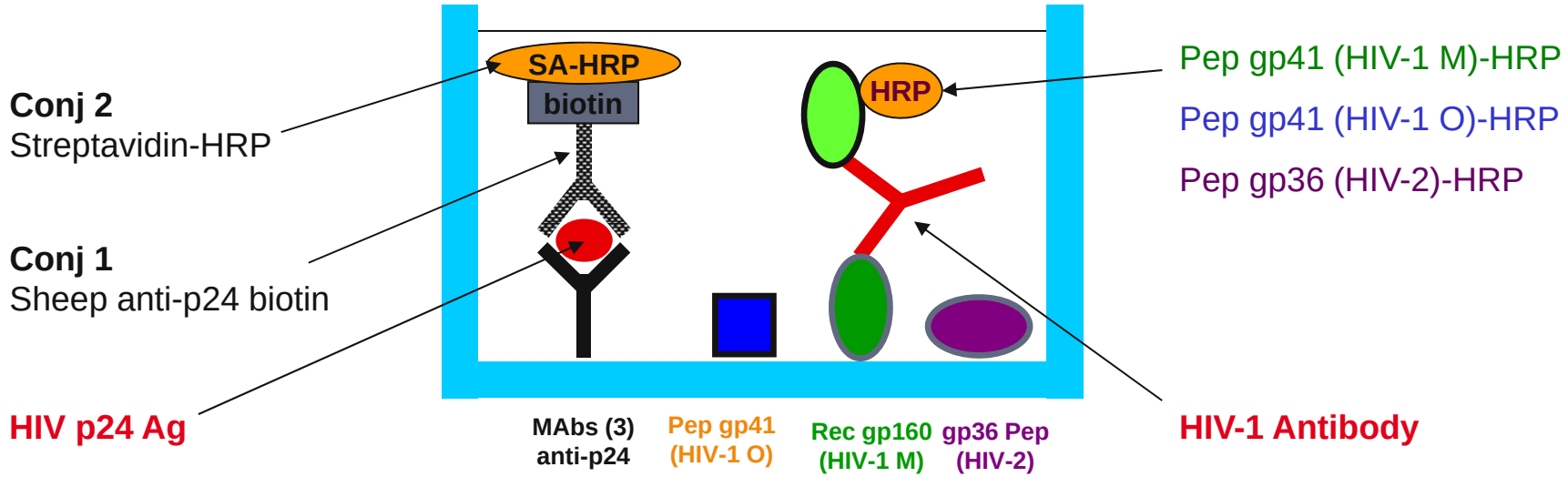
- GS HIV-1/HIV-2 *PLUS O* EIA – microplates and reagents
  3rd generation test using peptides and recombinant proteins

GS HIV COMBO Ag/Ab EIA – 4th Generation assay

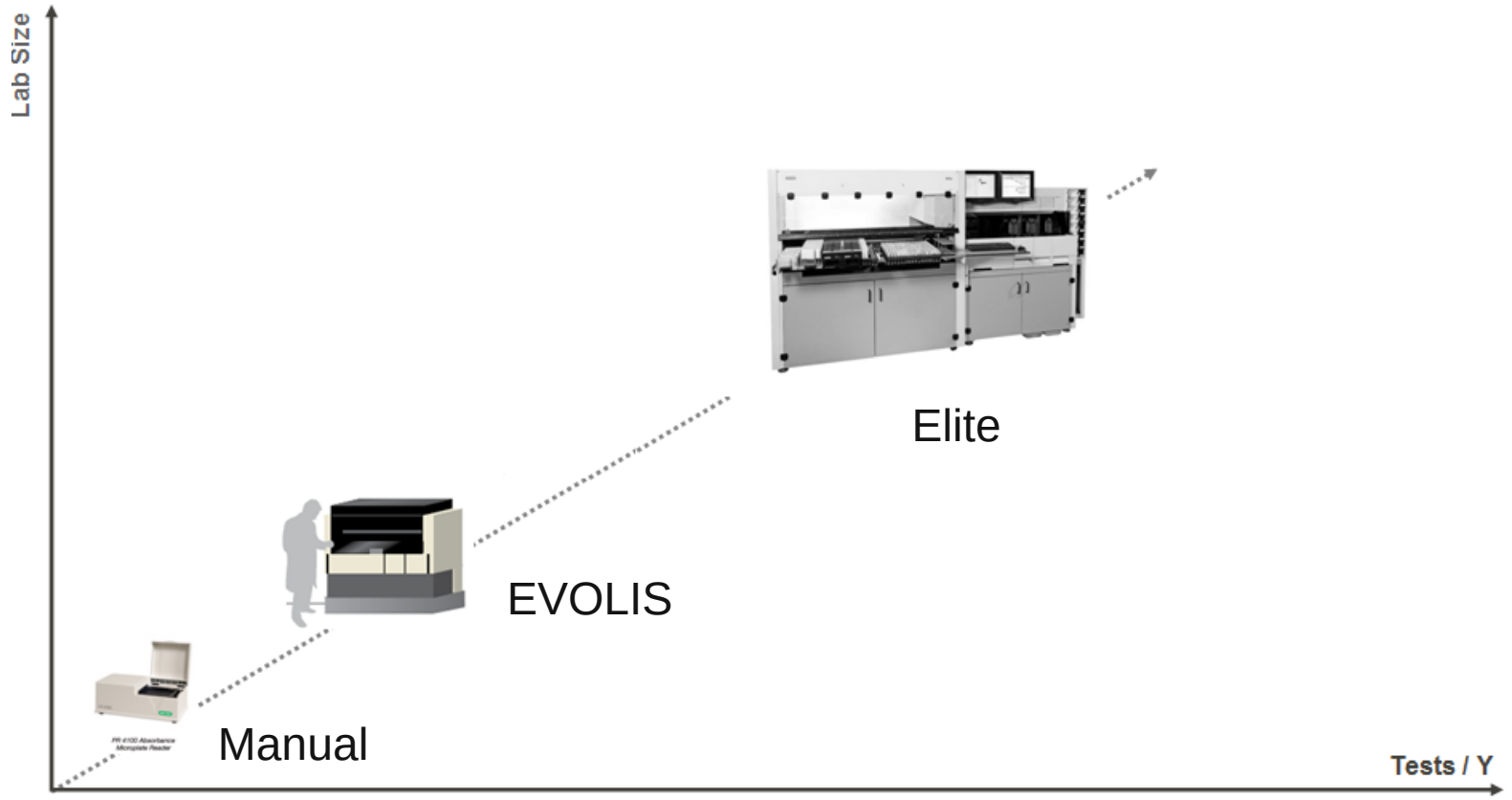
- Microwell schematic for simultaneous detection of HIV Antigen **and** Antibodies.

Antigen Detection Conjugates:

Antibody Detection Conjugates:



Bio-Rad Automated Systems- 4th Gen HIV Combo Ag/Ab EIA assay



HIV testing can be performed manually or with FDA approved automated instruments based on annual testing volumes.

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Bio-Rad GS HIV Combo Ag/Ab Test Panels

GS HIV Combo Ag/Ab EIA		
Panels	**Manual**	**Automated**
HIV-1 Positive Panel	**100 samples (x 1 replicate)**	**100 samples (x 1 replicate)**
HIV-2 Positive Panel	**100 samples (x 1 replicate)**	**100 samples (x 1 replicate)**
HIV antigen Positive	**100 samples (x 1 replicate)**	**100 samples (x 1 replicate)**
HIV Group O Positive	**4 samples (x 1 replicate)**	**4 samples (x 1 replicate)**
HIV Negative Panel	**100 samples (x 1 replicate)**	**100 samples (x 1 replicate)**
Seroconversion Panels	**20 Panels (152 samples x 2 replicates)**	**20 Panels (152 samples x 2 replicate)**
Dilution Panels	**20 HIV-1 Ab samples (20 x 4 levels x3 replicates)** **10 HIV-2 Ab samples (20 x4 levels x 3 replicates)** **10 HIV Ag samples (20 x 4 levels x 3 replicates**	**20 HIV-1 Ab samples (20 x 4 levels x3 replicates)** **10 HIV-2 Ab samples (20 x 4 levels x 3 replicates)** **10 HIV Ag samples (20 x 4 levels x 3 replicates)**
Reproducibility Panels	**20 samples** 5 days / 2 runs per day / 3 replicates per run (30 replicates/sample)	**20 samples** 5 days / 2 runs per day / 3 replicates per run (30 replicates/sample)
Precision Panel **(at one site)**	**20 samples** **20 days / 2 runs per day / 2 replicates per run** **(80 replicates/sample)**	**20 samples** **20 days / 2 runs per day / 2 replicates per run** **(80 replicates/sample)**

GS HIV Combo Ag/Ab 2x2 table with bootstrap 95% CI, manual vs. Elite

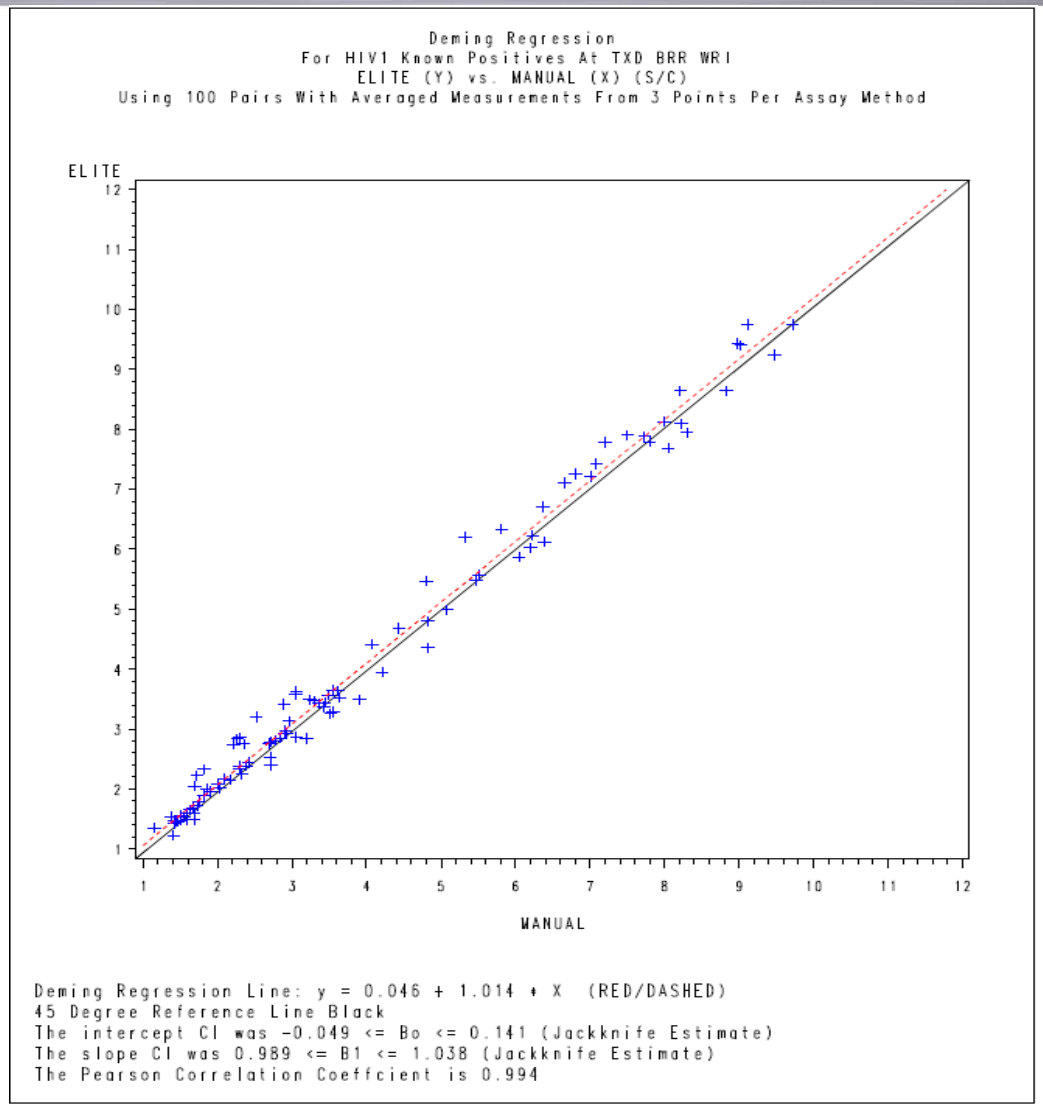
HIV Antigen Positive Panel			Elite Microplate System			Positive (+) % Agreement 95% Confidence Interval	Negative (-) % Agreement 95% Confidence Interval	Overall % Agreement 95% Confidence Interval
			Reactive	Non reactive	Total			
Manual	Averaged Across All Sites	Reactive	100	0	100	100% (100 / 100) 100% , 100%*	NA	100% (100 / 100) 100% , 100%*
		Nonreactive	0	0	0			
		Total	100	0	100			
	Site 1	Reactive	100	0	100	100% (100 / 100) 96.3% , 100%	NA	100.% (100 / 100) 96.3% , 100%
		Nonreactive	0	0	0			
		Total	100	0	100			
	Site 2	Reactive	100	0	100	100% (100 / 100) 96.3% , 100%	NA	100.% (100 / 100) 96.3% , 100%
		Nonreactive	0	0	0			
		Total	100	0	100			
	Site 3	Reactive	100	0	100	100% (100 / 100) 96.3% , 100%	NA	100% (100 / 100) 96.3 , 100%
		Nonreactive	0	0	0			
		Total	100	0	100			

The confidence intervals are created using bootstrap estimates for multiple sites

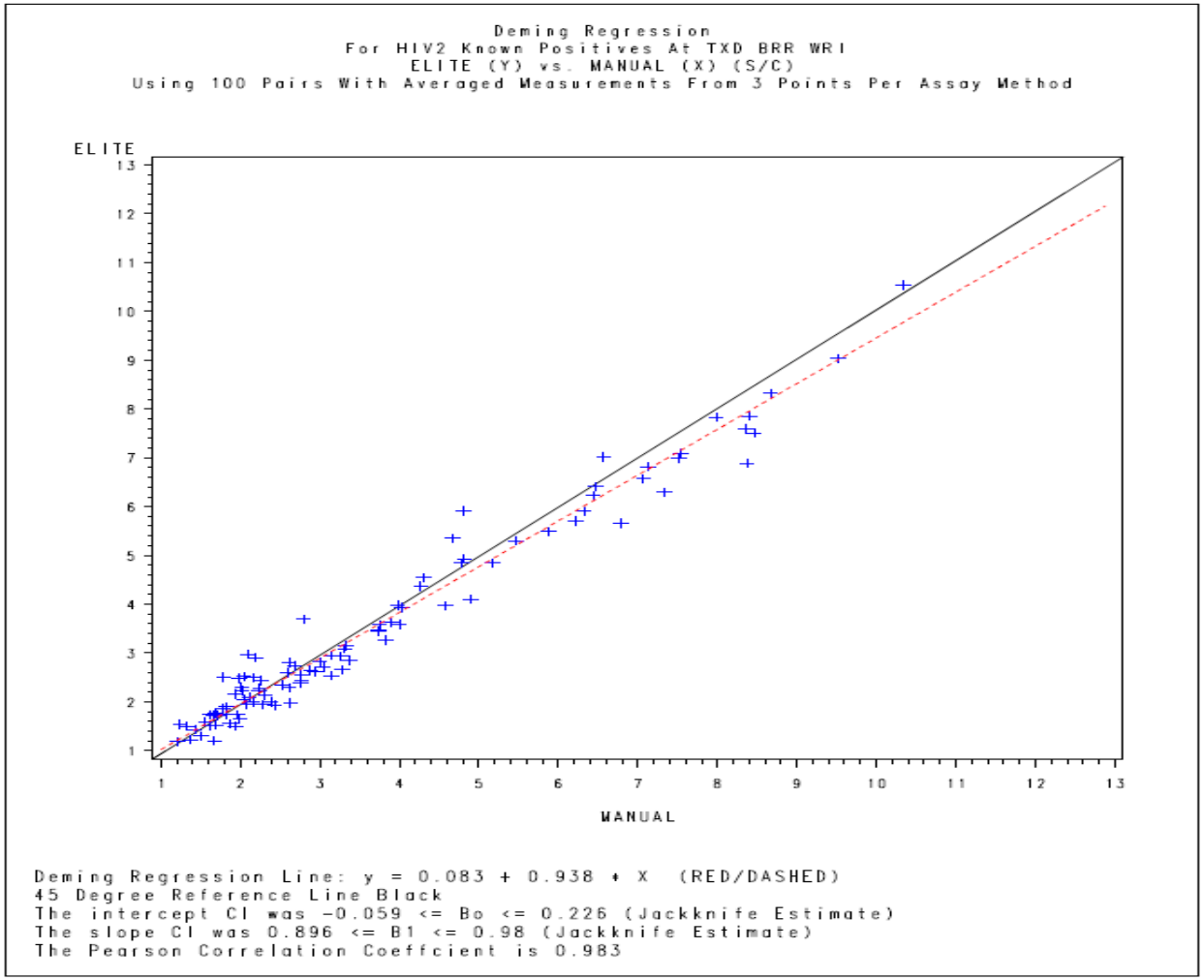
HIV-1 Antigen Dilution Panel
Mean Difference between Elite Microplate System and Manual System

Dilution Level Target S/CO	N	Elite Mean S/CO	Manual Mean S/CO	Mean Difference from Manual S/CO*	% Difference** From Manual*	Two-tailed p-value	Statistically Significant at p= 0.05?	Specificity Acceptance Criteria ≤0.332 S/CO Difference Pass/Fail	Sensitivity Acceptance Criteria ≤12.5% Difference Pass/Fail
Moderate Positive	90	4.296	4.328	-0.033	-0.76%	0.3761	NO	PASS	PASS
Low Positive	90	2.459	2.503	-0.044	-1.77%	0.0308	YES	PASS	PASS
Near Cutoff	90	1.508	1.521	-0.013	-0.83%	0.3102	NO	PASS	PASS
Below Cutoff	90	0.648	0.647	0.001	0.15%	0.8666	NO	PASS	PASS
Total	360	2.228	2.250	-0.022	-0.98%	0.0449	YES	PASS	PASS

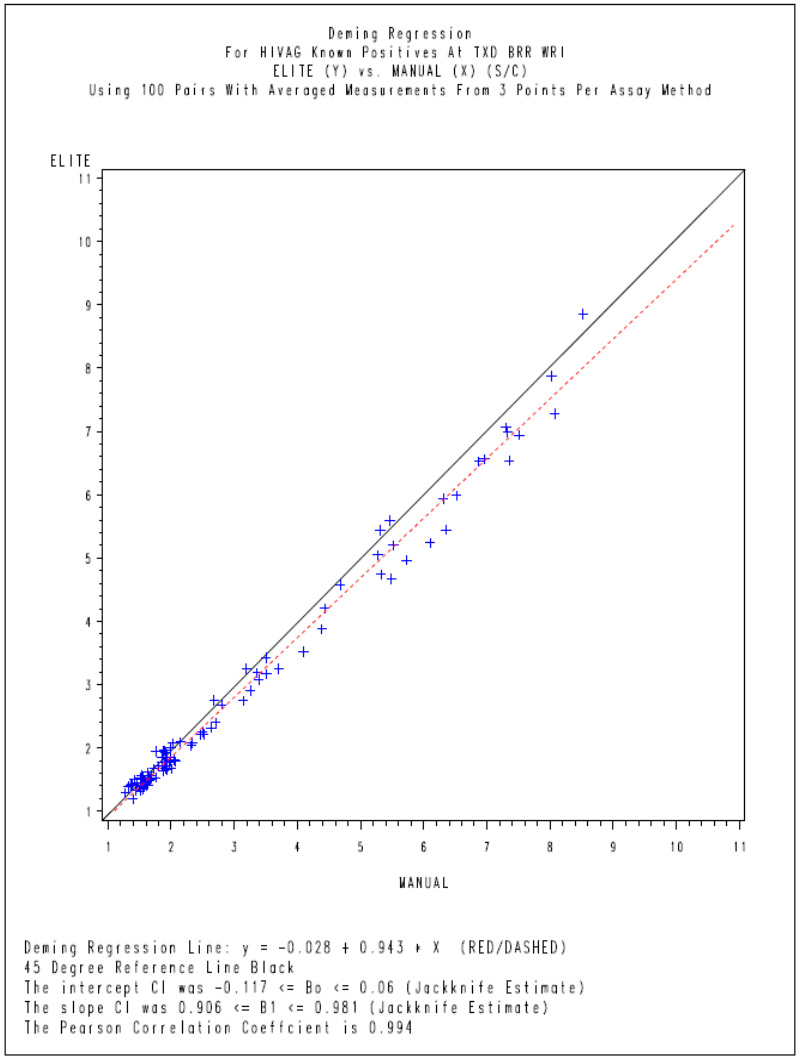
Deming Regression GS HIV Combo Ag/Ab EIA on Elite Automated System – HIV-1 Ab positives



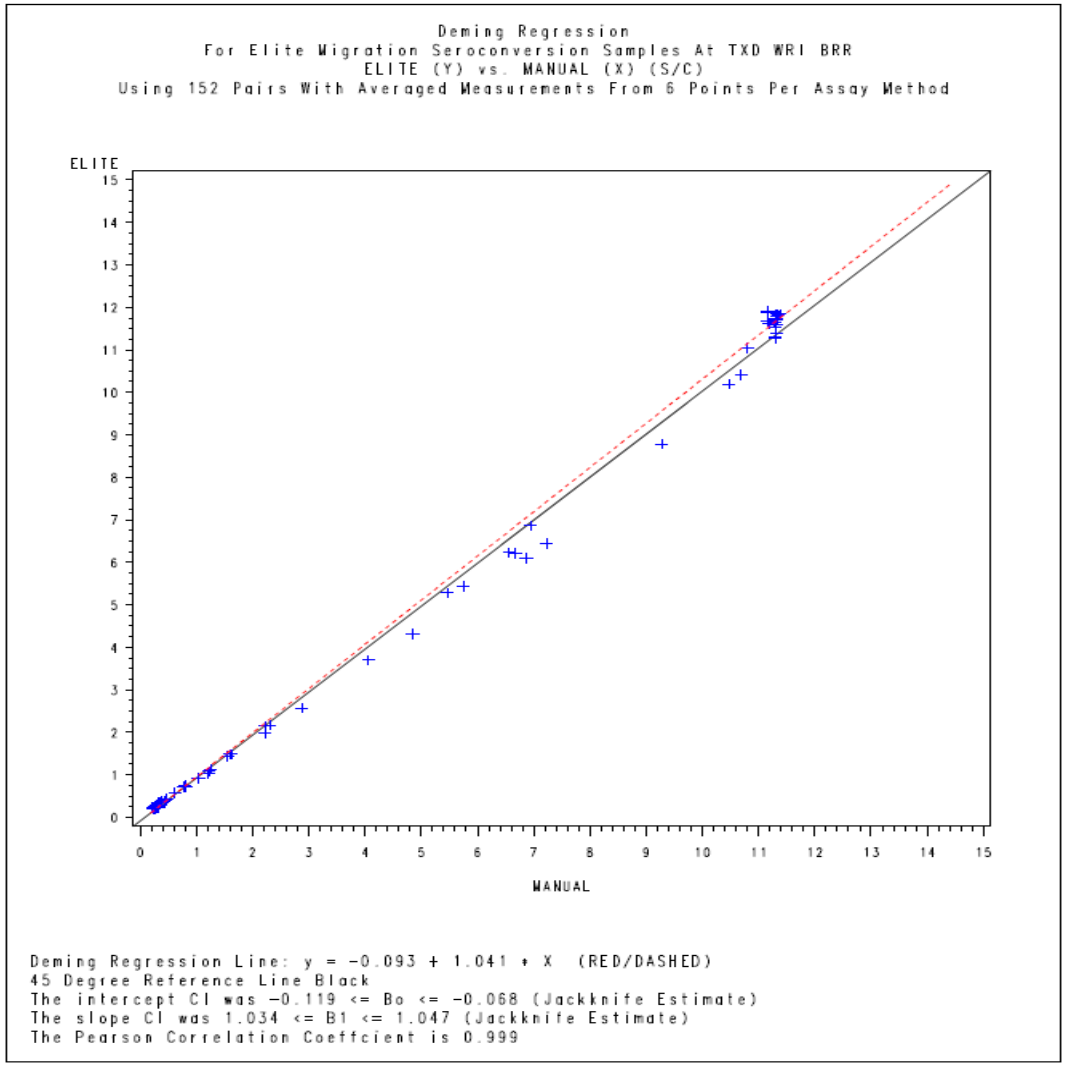
Deming Regression GS HIV Combo Ag/Ab EIA on Elite Automated System – HIV-2 Ab positives



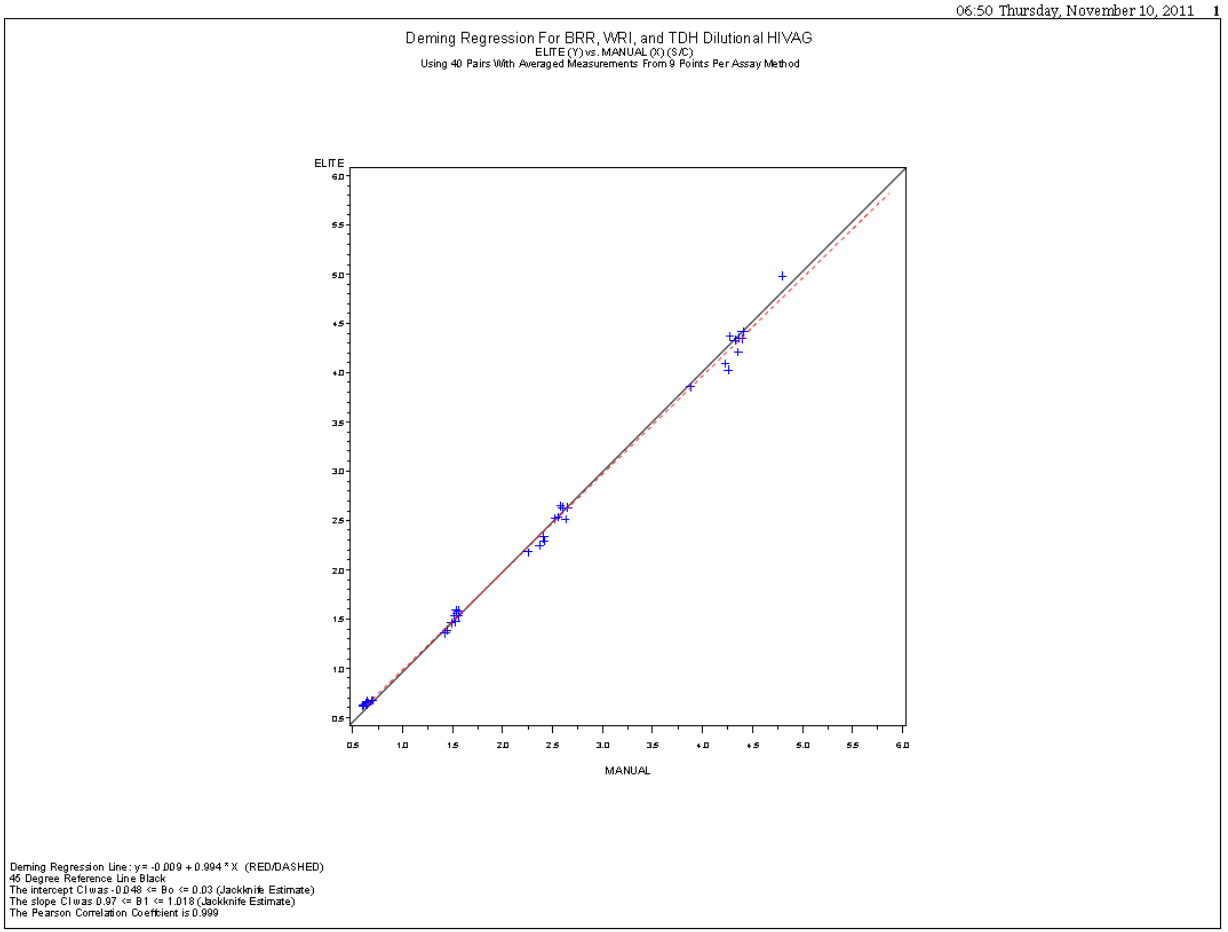
Deming Regression GS HIV Combo Ag/Ab EIA on Elite Automated System – HIV-1 Ag positives



Deming Regression for 20 HIV-1 S/C Panels, 3 sites with 4th Gen HIV Combo Elite Automated Testing



Deming Regression HIV-1 Ag Dilution Series 4th Generation GS HIV Combo Ag/Ab EIA –Manual vs. Automated Elite Instrument



Calculation of C5 and C95 4th Gen HIV Combo Ag/Ab EIA on Elite Automated System

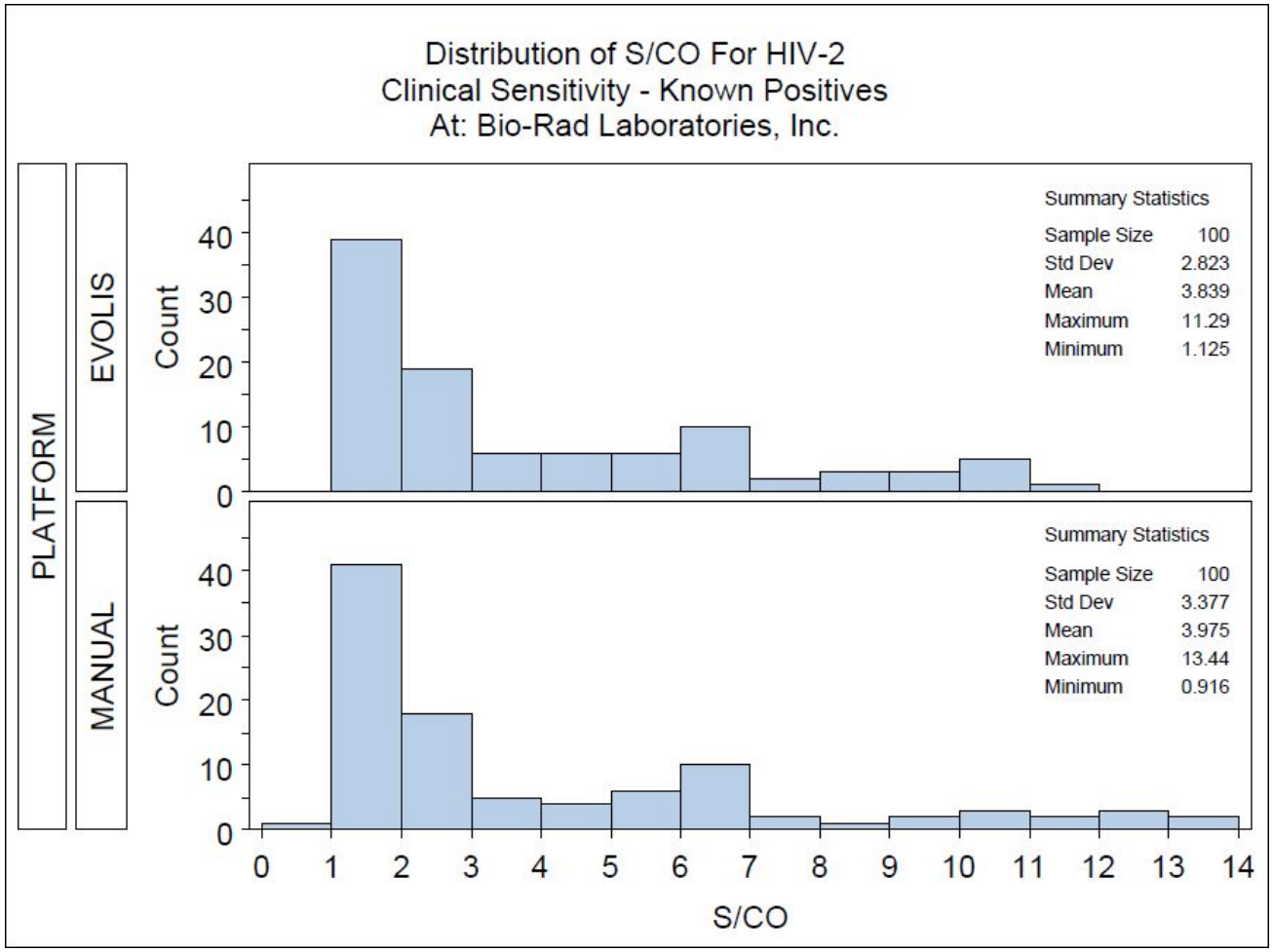
Panel Member	Manual System				Elite Microplate System			
	Within Run[2]		Total[3]		Within Run[2]		Total[3]	
	C_{95}	C_5	C_{95}	C_5	C_{95}	C_5	C_{95}	C_5
HIV-1 Moderate Positive (Serum)	1.069	0.940	1.192	0.861	1.122	0.902	1.241	0.837
HIV-1 Low Positive (Serum)	1.145	0.888	1.264	0.827	1.043	0.960	1.204	0.855
HIV-1 Moderate Positive (Plasma)	1.086	0.927	1.223	0.846	1.086	0.927	1.221	0.847
HIV-1 Low Positive Plasma	1.038	0.965	1.251	0.833	1.103	0.914	1.246	0.835
HIV-2 Low Positive (Serum)	1.145	0.888	1.490	0.752	1.120	0.903	1.501	0.750
HIV-2 Moderate Positive (Serum)	1.154	0.882	1.472	0.757	1.094	0.921	1.373	0.787
HIV-2 Moderate Positive Plasma	1.074	0.935	1.241	0.837	1.067	0.941	1.325	0.803
HIV-2 Low Positive (Plasma)	1.143	0.889	1.395	0.779	1.243	0.836	1.657	0.716
HIV1-Ag Moderate Positive (Serum)	1.041	0.962	1.132	0.895	1.052	0.953	1.139	0.891
HIV1-Low Positive Ag (Serum)	1.048	0.956	1.143	0.889	1.043	0.960	1.152	0.884
HIV1-Ag Moderate Positive (Plasma)	1.090	0.924	1.165	0.876	1.070	0.938	1.145	0.888
HIV1-Ag Low Positive (Plasma)	1.043	0.960	1.141	0.890	1.048	0.956	1.147	0.886
HIV Group O Positive (Serum)	1.134	0.894	1.551	0.738	1.120	0.903	1.539	0.741
HIV High Negative (Serum)	1.063	0.944	1.163	0.877	1.072	0.937	1.183	0.866
HIV High Negative (Plasma)	1.070	0.938	1.197	0.859	1.059	0.947	1.202	0.856
HIV-1 Moderate Control	1.074	0.935	1.172	0.872	1.097	0.918	1.195	0.860
HIV-2/O Moderate Control	1.072	0.937	1.197	0.859	1.074	0.935	1.308	0.810
Antigen Moderate Control	1.063	0.944	1.163	0.877	1.059	0.947	1.132	0.895
Cut Off Control	1.059	0.947	1.249	0.834	1.116	0.906	1.246	0.835
Negative Control	1.241	0.837	1.398	0.778	1.404	0.776	1.483	0.754

HIV-2 EIA Automated Specificity Testing of Blood Donors

Reactivity in Low Risk Normal Donor Population Tested on the EVOLIS™ Automated Microplate system

Site	Number Normal Donors	GS HIV-2 EIA			Repeatedly Reactive Samples		GS HIV-2 EIA Specificity	
		Non Reactive	Initially Reactive	Repeatedly Reactive	Multispot HIV-2 Reactive	Multispot HIV-1 Reactive	Specificity*	95% Confidence Interval
1	1,000	996 (99.6%)	4 (0.4%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	(998 / 1000) 99.8%	99.3%-99.9%
2	1,000	991 (99.1%)	9 (0.9%)	7 (0.7%)	0 (0.0%)	0 (0.0%)	(993 / 1000) 99.3%	98.6%-99.7%
3	1,000	991 (99.1%)	9 (0.9%)	9 (0.9%)	0 (0.0%)	0 (0.0%)	(991 / 1000) 99.1%	98.3%-99.5%
Total	3,000	2978 (99.3%)	22 (0.7%)	18 (0.6%)	0 (0.0%)	0 (0.0%)	(2982 / 3000) 99.4%	99.1%-99.6%

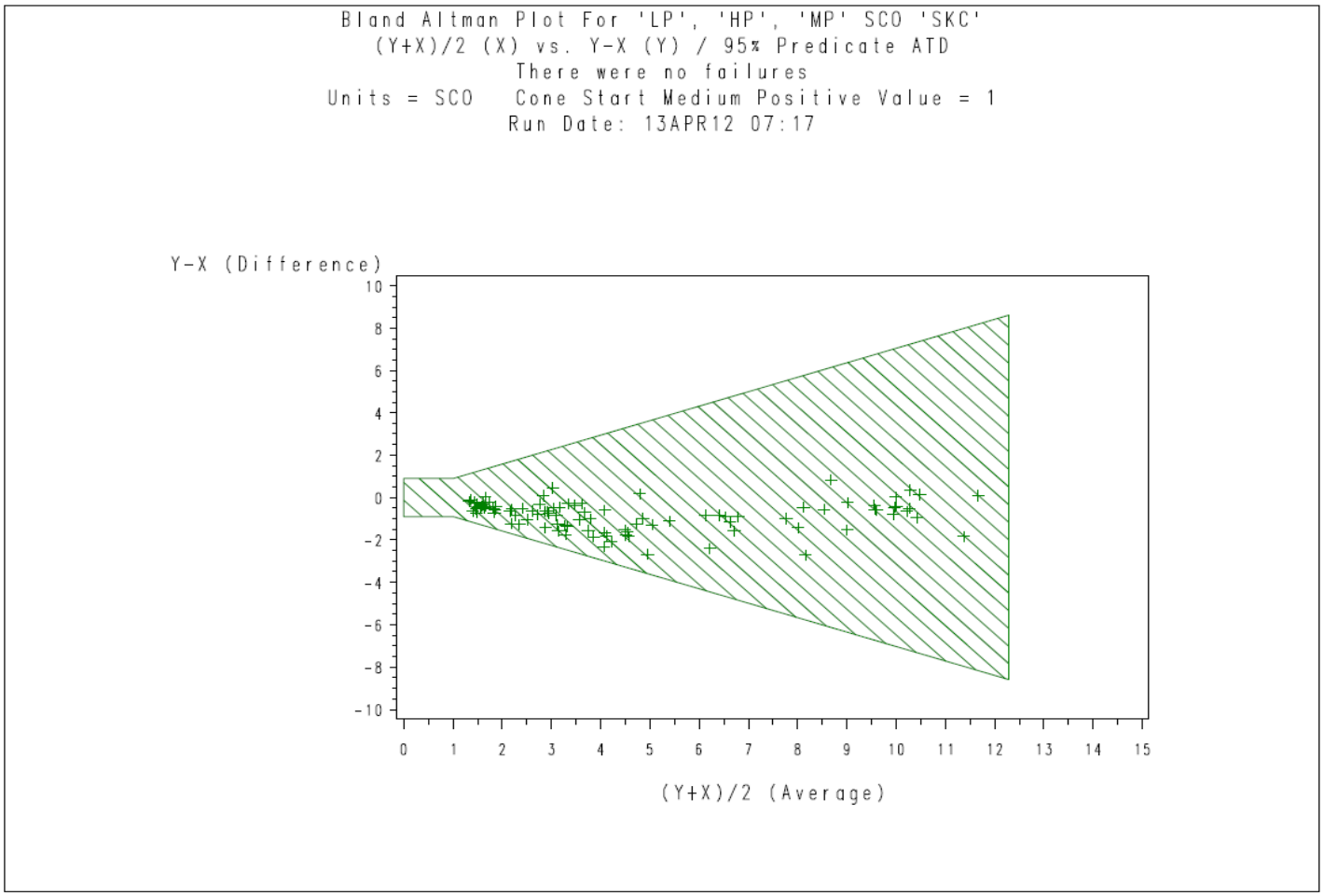
Histogram of HIV-2 antibody positives, manual vs. EVOLIS
Automated testing for HIV-2 EIA



10 member reproducibility panel testing with HIV-2 EIA on EVOLIS Automated instrument

Panel Member		N	Mean (S/C)	Within Run[1]		Between Run[2]		Between Day[3]		Total[4]	
				SD	%CV	SD	%CV	SD	%CV	SD	%CV
V2R0001	HIV-2 positive serum	30	2.92	0.193	6.6 %	0.000	0.0 %	0.106	3.6 %	0.220	7.5 %
V2R0002	HIV-2 low positive serum	30	1.74	0.032	1.9 %	0.058	3.3 %	0.053	3.0 %	0.085	4.9 %
V2R0003	HIV-2 positive plasma	30	3.10	0.168	5.4 %	0.000	0.0 %	0.115	3.7 %	0.204	6.6 %
V2R0004	HIV-2 low positive plasma	30	1.74	0.079	4.5 %	0.051	2.9 %	0.032	1.9 %	0.099	5.7 %
V2R0005	HIV-2 high negative serum	30	0.66	0.049	7.4 %	0.030	4.6 %	0.000	0.0 %	0.057	8.7 %
V2R0006	HIV-2 high negative plasma	30	0.65	0.069	10.6 %	0.000	0.0 %	0.000	0.0 %	0.069	10.6 %
V2R0007	HIV non-reactive serum	30	0.36	0.042	11.6 %	0.005	1.4 %	0.008	2.1 %	0.043	11.9 %
V2R0008	HIV non-reactive plasma	30	0.26	0.033	12.4 %	0.006	2.2 %	0.007	2.7 %	0.034	12.8 %
V2R0009	HIV-2 positive control	30	7.46	0.323	4.3 %	0.053	0.7 %	0.116	1.6 %	0.347	4.7 %
V2R0010	HIV negative control	30	0.29	0.033	11.5 %	0.000	0.0 %	0.006	1.9 %	0.034	11.7 %

MONOLISA™ Anti-HBs EIA (quantitative claim in mIU/ml) Manual vs. EVOLIS Automated testing- Bland Altman Plot



Conclusion:

- The FDA draft Guidance on Migration Studies has been used successfully by a number of IVD manufacturers to migrate FDA approved or licensed assays from “Old” to “New” systems
- It is key that you have a strong R&D or Clinical Research department that can prepare the required analytical panels for migration testing.
- A statistician (company employee or consultant) that very familiar with this guidance is critically important.
- Migration statistics can be performed using Excel, Minitab or SAS software packages. Let FDA know which one you plan to use.
- Migration studies can be difficult analytical studies to perform but are preferable to full prospective or retrospective clinical studies
- The Final Migration Guidance should be published “shortly”