Benchmarking Analytical Performance: Comparison of Third Party Quality Controls

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Executive Summary

Laboratories are under increasing pressure to do “more with less,” and simultaneously produce patient test results of the highest analytical quality. Patient test results are routinely assessed by quality controls and the expense of running quality controls has a significant impact on the bottom line of every laboratory budget.

The investment in control materials has long been sacrosanct, with the common assumption that differences in the cost of control materials equate to differences in quality. This assumption has rarely been tested.

In this study, laboratories tested two different control materials simultaneously and measured their performance using Sigma-metrics. Thirteen chemistry assays, six urine assays and twelve immunoassays were evaluated with Bio-Rad and Technopath controls. The performance was measured on the Six Sigma scale, a powerful benchmark used in manufacturing, industry, and healthcare. Contrary to conventional expectations, the data demonstrated that the controls had comparable performance. The performance of the Technopath and Bio-Rad controls, as assessed by a Six Sigma tool (Method Decision Chart), showed a high degree of comparability and very little systematic difference. The premium control did not deliver premium performance - any additional expense on the premium control was simply additional outlay without a commensurate performance gain.

Through the use of Sigma-metric benchmarking as well as traditional statistical F-tests, Technopath controls were found to be comparable to Bio-Rad controls. This finding provides an opportunity for laboratories to consider efficiencies and consolidation without sacrificing quality.

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Introduction

Choosing a control material is as important as choosing an instrument, method, and assay. Laboratories need to consider multiple factors when selecting quality controls. One key consideration is the ability of the control to correctly monitor the performance of the method on the basis of the inherent analytical quality of an assay. This can be done objectively and quantitatively using Sigma-metrics. If different controls demonstrate essentially the same analytical performance, they are comparable. When controls demonstrate comparability, they can be used interchangeably.

What is a control material?

The International Organization for Standardization (ISO) and the Clinical Laboratory Standards Institute (CLSI) have a specific definition for a control material:

> *"a device, solution, or lyophilized preparation intended for use in the quality control process to monitor the reliability of a test system and to maintain its performance within established limits; NOTE: The expected reaction or concentration of analytes of interest are known within limits ascertained during preparation and confirmed in use."*[1,2]

The official terminology is somewhat at odds with the common vernacular employed with control materials; often they are referred to simply as "controls" or sometimes "control solutions" but they may be referenced more formally as "external controls" (because they are external to the instrument or method, not built into the test system) or even as "reference samples" or "surrogate samples."

Regardless of terminology, when laboratory professionals discuss controls, they generally mean solutions available in liquid, frozen, or lyophilized form. These controls are used daily and often two or three times a day. Ideally, controls are commutable, that is, they mimic the analytical response of fresh patient samples. Many controls are not commutable because they undergo a manufacturing process, for example, lyophilization, that alters their nature. Related to commutability but different is the problem of matrix effects; a control may produce a falsely low or high result with a specific assay due to the presence of some interfering substance, but the assay itself will not demonstrate this problem with actual patient specimens.

What aspects of controls are important?

Choosing a control material is as important as choosing an instrument, method or assay. Multiple factors need to be considered, including the following identified by Cooper et al.[3]:

- Liquid vs. lyophilized
- Manufacturer vs. 3rd party
- Patient pools vs. commercial materials
- Commutability
- Matrix effects
- Target values and decision levels
- Bottle values vs. in-house assigned control limits

While all of these factors are important, they are nevertheless secondary to the central utility of a control. Whether or not it is convenient or inexpensive to use a control should not be the first priority; whether the control material works correctly should be.

What's the core competency of a control material?

For all the different factors that impact the choice of control materials, the first priority in evaluating control materials is to ensure they can be trusted to correctly monitor the analytical performance of the methods being tested.

The two core purposes of controls are to:

1. Identify out-of-control situations in method performance (error detection).
2. Avoid misidentifying in-control situations as out-of-control (false rejection).

Few laboratories have assessed these functional capabilities of their control materials. Six Sigma metrics provide a useful tool to do this objectively and quantitatively and establish analytical performance benchmarks, which can then be used to make meaningful comparisons. When different controls show essentially the same analytical performance, labs can confidently use them interchangeably.

Methods: What is Six Sigma? And how does it apply to control materials?

Six Sigma is a well-known quality management approach that uses multiple tools to achieve the goal of reducing errors and defects in any process. Six Sigma began in companies like General Electric and Motorola, but has spread to service sectors and even to healthcare institutions and the clinical laboratory.

The central focus of Six Sigma is to measure the number of defects-per-million opportunities (DPM, or DPMO) in any process. This DPM rate is then converted into a simple scale of 0 to 6, which is called the Sigma-metric of the process. Achieving Six Sigma on the short term scale means that only 3.4 defects are expected per million outcomes of the process. To put it in laboratory terms, a Six Sigma test on that scale would only be expected to produce about 4 defective results per million tests run. At the quality level of Six Sigma, processes become highly efficient and effective, reducing the effort required to maintain them and maximizing the reliability and profitability of that process.

On the other hand, a three Sigma process is expected to produce more than 67,000 defects per million outcomes. Outside of healthcare, a process that is below three Sigma is often considered too costly and defect-prone to operate efficiently. In business and manufacturing, a process below three Sigma would be identified as a target for radical improvement, redesign or replacement.

For analytical processes, the Sigma-metric is calculated using data obtained from control materials. Imprecision from routine control performance and Bias (Trueness) can be obtained by comparing the control mean of the laboratory with the control mean of the peer group. Then a third variable is used, a quality requirement in the form of an allowable Total Error (TEa), which represents the goal for performance. These three variables are arranged in the following equation to calculate the Sigma-metric:

$$\textbf{Sigma-metric} = (TEa - Bias) / CV$$

[all parameters expressed as %]

More detailed discussion of the Sigma-metric equation can be found in the literature and reference manuals[4]. In addition, there are widely available guidelines that document best practices for obtaining the most appropriate estimates of each variable in the equation[5].

Materials and Methods: Control Performance Data

Five multiconstituent controls (MCC) from Technopath Manufacturing Ltd (Ballina, Ireland) were evaluated in the Familiarization study. For immunoassays, the Multichem IA Plus (3 levels) and the Multichem WBT (3 levels) were evaluated. For clinical chemistry assays, the Multichem S Plus (3 levels), the Multichem P (1 level) and Multichem U (2 levels) were evaluated. The Multichem controls are prepared from human serum, urine or whole blood to which purified biochemical material (extracts of human and animal origin), chemicals, drugs, preservatives and stabilizer have been added. Multichem S Plus, P, IA Plus and WBT are provided in liquid form and stored frozen (-20 to -80°C) until use. Once thawed, the controls are stored at 2-8°C; most analytes are stable for 10 days, with exceptions noted in the lot specific data sheets. The Multichem U controls are provided in liquid form and stored at 2-8°C. Once the material is opened, it should be stored tightly capped at 2-8°C and is stable for 30 days unless otherwise stated in the lot specific data sheets.

The evaluation was performed at the following four sites: Toronto General Hospital, Toronto, Canada, Hôpital Tenon, Paris, France; Marienhospital, Stuttgart, Germany; Ospedale Civile, Sondrio, Italy. Instrumentation at the four sites included eight ARCHITECT *i*2000SR, one ARCHITECT *i*1000SR, seven ARCHITECT *c*8000 and one ARCHITECT *c*16000 instruments.

Technopath controls were tested once daily for a minimum of thirty days for all assays that the sites routinely perform. Data for the laboratory's routine QC control materials were also collected. The routine QC controls included Bio-Rad Liquichek Unassayed Chemistry controls, Liquichek Lipid, Liquichek Ethanol/Ammonia, Liquid Assayed Multiqual, Liquichek Urine Chemistry, Liquichek Immunoassay Plus and Liquicheck Cardiac Marker. In addition to Bio-Rad controls, some sites utilized Abbott single constituent controls (SCCs) or Abbott multi-constituent controls produced by Bio-Rad (MCCs).

All data were collected through the AbbottLink remote monitoring software and analyzed using SAS version 9.2 or higher. Descriptive statistics (n, mean, standard deviation, %CV and range) were provided for each control level by analyte and instrument. Data presented here are for thirteen clinical chemistry serum assays, six clinical chemistry urine assays and twelve serum immunoassays with Multichem S Plus, U and IA Plus controls. The imprecision estimates were used for Sigma-metric calculations.

Bias was determined by calculating the peer mean of the laboratories using the control materials. Individual instrument means were then compared against the peer mean and that difference was converted into a percentage bias. These bias estimates were used in Sigma-metric calculations. Given the variety of controls, it was considered expedient and equitable to compare against the peer means, instead of different assayed or assigned means.

Quality requirements were chosen from the US CLIA proficiency testing criteria published in the Federal Register listed below in Table 1.

Chemistry Analyte	Total Allowable Error (TEa) from CLIA
Alanine Aminotransferase (ALT)	± 20%
Aspartate Aminotransferase (AST)	± 20%
Bilirubin, Total	± 0.4 mg/dL or ± 20% (whichever is greater)
Chloride	± 5%
Cholesterol, Total	± 10%
Creatinine (enzymatic)	± 0.3 mg/dL or ± 15% (whichever is greater)
Creatinine (picrate)	± 0.3 mg/dL or ± 15% (whichever is greater)
Glucose	± 6 mg/dL or ± 10% (whichever is greater)
Potassium	± 0.5 mmol/L
Protein, Total	± 10%
Sodium	± 4 mmol/L
Triglycerides	± 25%
Urea	± 2 mg/dL or ± 9% (whichever is greater)

Table 1. Total Allowable Errors for chemistry analytes found in the CLIA Proficiency Testing Criteria[6].

CLIA does not provide proficiency testing criteria for analytes in urine. Therefore, quality requirements for the urine assays were chosen mainly from the Royal College of Pathologists of Australasia (RCPA) Allowable Limits of Performance (ALP)[7]. For Urea, the total allowable error was selected from the Desirable specifications for Total Allowable Error derived from Biologic Variation[8]. In many cases, while the RCPA goal is split into two specifications (one for the lower end of the range that is unit-based, and one for the higher end of the range that is percentage-based), the measured data points were all on the higher end, so the unit-based goal did not need to be applied. The quality requirements for urine analytes are shown in Table 2.

Urine Analyte	Total Allowable Error (TEa)	TEa Source
Chloride	± 2.0 mmol/L < 20.0 mmol/L ± 10% > 20.0 mmol/L%	RCPA
Creatinine	± 0.5 mmol/L < 5.0 mmol/L ± 10% > 5.0 mmol/L	RCPA
Glucose	± 1.0 mmol/L < 10.0 mmol/L ± 10% > 10.0 mmol/L	RCPA
Potassium	± 2.0 mmol/L < 20.0 mmol/L ± 10% > 20.0 mmol/L	RCPA
Sodium	± 2.0 mmol/L < 20.0 mmol/L ± 10% > 20.0 mmol/L	RCPA
Urea	± 22.1%	Biologic Variation Database

Table 2. Total Allowable Errors for Urine analytes.

Finally, for many immunoassay analytes, CLIA again does not provide total allowable errors. In this case, quality requirements were chosen from the Royal College of Pathologists of Australasia (RCPA) Allowable Limits of Performance (ALP)[7], the Desirable specifications for Total Allowable Error derived from Biologic Variation[8] and the German RiliBÄK guidelines[9] as well as the minimum specifications as identified by the Spanish consortium of EQA providers[10]. For Vitamin D, a publication provided an estimate of the minimum allowable total error based on biologic variation[11]. Table 3 summarizes the requirements for immunoassays.

Immunoassay Analyte	Total Allowable Error (TEa)	TEa Source
Second Generation Testosterone	± 23%	Spanish Minimum Guidelines
beta hCG	± 30%	RiliBÄK
CA 19-9	± 46.3%	Biologic Variation Database
CEA	± 24.7%	Biologic Variation Database
Estradiol	± 26.9%	Biologic Variation Database
FSH	± 21.2%	Biologic Variation Database
Free T3	± 24.0%	RiliBÄK
Free T4	± 24.0%	RiliBÄK
TSH	± 23.7%	Biologic Variation Database
Total PSA	± 33.6%	Biologic Variation Database
Troponin I	± 27.9%	Biologic Variation Database
Vitamin D	± 32.2%	Minimum TEa[11]

Table 3: Total Allowable Errors for Immunoassay analytes.

Sigma-metrics were calculated for all levels for all control levels, for all controls, and all instruments. The Sigma-metrics were then plotted on Method Decision Charts for each analyte. The Method Decision Chart[7] is a graphic assessment tool, which allows a simple visual check for comparability. A specific Method Decision Chart was constructed when the total allowable error was a fixed percentage. When the total allowable error was a mixed goal (i.e. a lower range goal in units and an upper range goal in percentage), the results were plotted on a normalized Method Decision Chart.

The summary tabulation of Sigma-metric performance took into consideration the fact that more levels were tested with the Technopath controls than with Bio-Rad controls. Consequently, this evaluation assessed the percentage of control levels achieving different levels of Sigma performance rather than the absolute number of control levels.

Furthermore, the Sigma-metric values were combined to calculate standard deviation and variance. Given that all values exceeding Six Sigma have the same operational outcome any Sigma-metric greater than 6 was assigned the value of 6. A simple statistical F-test was then used to compare the variances of the controls.

Results

The results of the Sigma-metric analysis for each analyte are shown in the Method Decision charts (Appendix, Figures A1-A32). The Method Decision Charts show a remarkable similarity among controls for different methods. Assay performance appears to be essentially independent of the controls being used.

World Class Six Sigma performance is seen with both Technopath and Bio-Rad controls on the majority of the Sigma-metric data for ALT, AST, Total Bilirubin, Creatinine (both Picrate and Enzymatic), Glucose, Potassium, Triglycerides, Total Protein, Urine Glucose, Urine Potassium, Urine Urea, and Total PSA. For Chloride, Sodium, Urea, Urine Creatinine (Picrate and Enzymatic), CA 19-9, CEA, Estradiol, Free T4, and Vitamin D, the Technopath and Bio-Rad controls display similar Sigma performance.

For a few tests, it appeared that Bio-Rad controls exhibited less bias than the Technopath controls: Total Cholesterol, Second Generation Testosterone, and Beta hCG. However, there were a few tests where the situation was reversed and the Technopath controls exhibited less bias: FSH, TSH, Total PSA, and Troponin I.

There were no analytes for which there appeared to be significantly different performance for all data points between the two controls.

Summary of Sigma Performance

The Sigma-metrics of all the analytes are summarized in the tables and charts below. The Sigma values for Technopath and Bio-Rad are comparable, varying only in some instances by a few percentage points. Overall, greater than 55% of the results were 6 Sigma for both controls.

Sigma-metric comparison of Chemistry controls

Control	Sigma-Metric						Control	Sigma-Metric					
Technopath	**6**	**5**	**4**	**3**	**<3**	**Total**	**BioRad**	**6**	**5**	**4**	**3**	**<3**	**Total**
ALT	15	3	2		1	21	ALT	6	3		1	4	14
AST	19		2			21	AST	12	1	1			14
Bilirubin, Total	14	4	3			21	Bilirubin, Total	9	4	1			14
Chloride	12	5	1	3		21	Chloride	5	3	2	4		14
Cholesterol, Total	7	3	5	3		18	Cholesterol, Total	9	2	2			13
Creatinine, Enzymatic	5			1		6	Creatinine, Enzymatic	3	1				4
Creatinine, Picrate	10		1	1		12	Creatinine, Picrate	7	1				8
Glucose	13	5	1	2		21	Glucose	9	2	1	2		14
Potassium	18	2	1			21	Potassium	12	1	1			14
Sodium		6	3	5	7	21	Sodium			3	7	4	14
Total Protein	10		3	1	1	15	Total Protein	8		1			9
Triglycerides	15					15	Triglycerides	10					10
Urea	1	2	4	5	9	21	Urea		1	3	3	7	14
Total	**139**	**30**	**26**	**21**	**18**	**234**		**90**	**19**	**15**	**17**	**15**	**156**
%	59.4	12.8	11.1	9.0	7.7			57.7	12.2	9.6	10.9	9.6	

Table 4. Breakdown of chemistry analytes and distribution of performance of controls. Note that there were 234 total control levels measured for the Technopath controls, while only 156 were measured for the Bio-Rad controls.

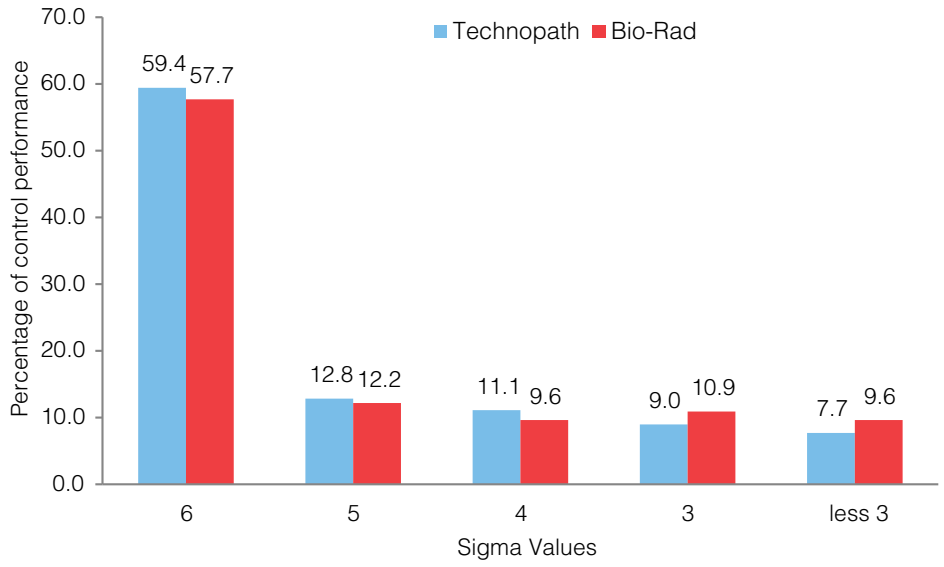

Figure 1. The graphic summary of the Sigma-metric breakdown of the chemistry control performance. A majority of the performance measured by both control materials is Six Sigma. The other Sigma categories are also very similar from control to control.

Sigma-metric comparison of Urine controls

Control	Sigma-Metric						Control	Sigma-Metric					
Technopath	**6**	**5**	**4**	**3**	**<3**	**Total**	**BioRad**	**6**	**5**	**4**	**3**	**<3**	**Total**
Chloride	11	1	1	1	0	14	Chloride	13	1		0	0	14
Creat Enzymatic U	2		2			4	Creat Enz U	2	1	1			4
Creat Picrate U	3	1	2		2	8	Creat Picrate U	3	0	2	2	1	8
Glucose	8	1	2	1	2	14	Glucose	10	4	0	0		14
Potassium	11	1	0	2		14	Potassium	10	4	0			14
Sodium	10		3	0	1	14	Sodium	11	0	1	1	1	14
Urea	12	1	0	1		14	Urea	10	2	1	1		14
Total	**57**	**5**	**10**	**5**	**5**	**82**		**59**	**12**	**5**	**4**	**2**	**82**
%	69.5	6.1	12.2	6.1	6.1			72.0	14.6	6.1	4.9	2.4	

Table 5. Breakdown of urine analytes and distribution of performance of controls.

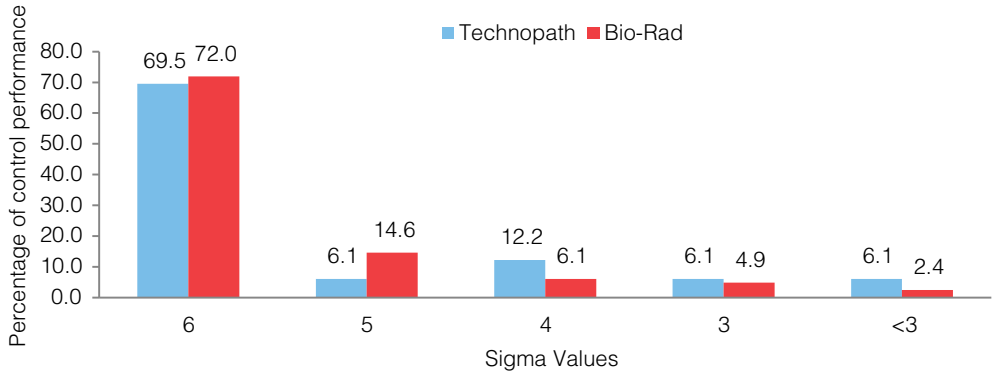

Figure 2. The graphic summary of the Sigma-metric breakdown of the urine control performance. A majority of the performance measured by both control materials is Six Sigma. The other Sigma categories are also similar from control to control.

Sigma-metric comparison of Immunoassay controls

Control	Sigma-Metric						Control	Sigma-Metric					
Technopath	**6**	**5**	**4**	**3**	**<3**	**Total**	**BioRad**	**6**	**5**	**4**	**3**	**<3**	**Total**
2nd Generation Testosterone	1	0	2	1	2	6	2nd Generation Testosterone	0	0	1	1	0	2
CEA	3	3	0	2	1	9	CEA	1	1				2
Estradiol	5	2	1	1		9	Estradiol	5	1			2	8
FSH	6	3				9	FSH	1	0	1	1	2	5
Free T3	3	4	5	2	1	15	Free T3	1		1	1	2	5
Free T4	4	4	3	2		13	Free T4	5	1	1			7
TSH	10	2	4	2		18	TSH	3	2	1	1		7
Total PSA	10	2				12	Total PSA	2	1		2		5
beta hCG	4	2		2	3	11	beta hCG	2	1		2	1	6
Troponin I	5	2	5	2	4	18	Troponin I	5			1	4	10
Vitamin D	1		1			2	Total Protein	2		1			3
Total	**52**	**24**	**21**	**14**	**11**	**122**		**27**	**7**	**6**	**9**	**11**	**60**
%	42.6	19.7	17.2	11.5	9.0			45.0	11.7	10.0	15.0	18.3	

Table 6. Breakdown of immunoassay analytes and distribution of performance of Technopath and Bio-Rad controls. There are over twice as many data points were available for the Technopath controls than for Bio-Rad. Note that the data for the MCC and SCC controls are not included in this table. Data for CA 19-9 is not included since there was no Bio-Rad data for comparison.

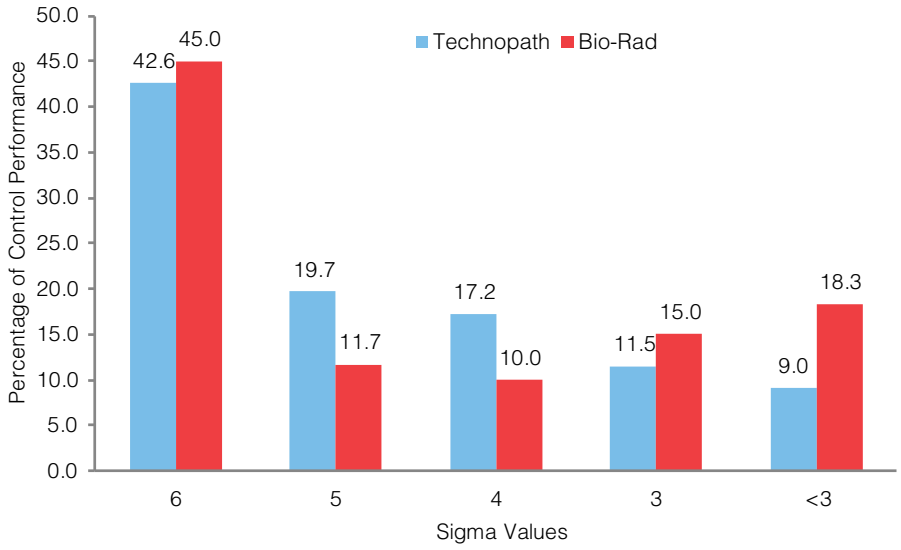

Figure 34. The graphic summary of the Sigma-metric breakdown of the immunoassay control performance. A majority of the performance measured by both control materials is above five Sigma. There are similar percentages of metrics in the 5 to 6 Sigma categories, but toward the lower end of the Sigma-scale, specifically below 3 Sigma, the Bio-Rad controls have significantly more values than Technopath.

In addition to these summaries of Sigma performance, an F-test of variance was performed for the Sigma-metrics of each analyte to determine if there was a statis tical difference between the variance of the control materials. For more than two-thirds of the analytes, the variances were the same indicating that the controls have similar variability. The variances were also the same for six other tests when the Sigma-metrics were simplified (i.e., all metrics 6 or higher were considered as 6, since for practical purposes their differences were insignificant). For the three analytes that still had significant differences in variance after Sigma simplification, it was determined that these were primarily caused by one or two outliers. When these data points were eliminated, the variances were statistically similar. None of the analytes exhibited a systematic difference across all the testing laboratories.

Analytes that passed the F-test (23)	Analytes that passed a simplified F-test (6)	Analytes where one or more outliers had to be excluded before the F-test was passed (3)
Creatinine Enzymatic, Creatinine Picrate, AST, Total Bilirubin, Glucose, Potassium, Total Protein, Sodium, Triglycerides, Urea, Urine Glucose, Urine Potassium, Urine Urea, Urine Creatinine Picrate, Second Generation Testosterone, CA 19-9, CEA, Estradiol, Free T4, TSH, beta hCG, Troponin I, Vitamin D	ALT, Cholesterol, Urine Chloride, Urine Creatinine Enzymatic, FSH, Total PSA	Chloride, Urine Sodium, Free T3

Discussion

Evaluating control material performance is a challenge because the measurement is also dependent upon the method used to test the sample. Since the vast majority of control materials are not trueness (accuracy) controls – that is, they are not traceable to a reference or true target value – the most one can expect is comparability or similarity in the values obtained from one control versus another.

The study demonstrated that the Technopath and Bio-Rad controls were very similar though not identical. The small differences observed with certain control concentrations, instruments, and laboratories were not unexpected given the nature of random variation. The important assessment, however, was the aggregate, overall performance, which indicated that the controls could be used interchangeably without causing dramatic changes in the measured performance of assays on the ARCHITECT systems. Labs can have confidence that they will see comparable performance with Technopath controls if they switch from Bio-Rad controls.

Limitations

The lack of traceability for control materials, while expected, is nevertheless a shortcoming of this study. We can only determine if the controls produce similar results, not whether or not the controls are getting the right result. However, because control materials are generally used to estimate imprecision, this is an expected shortcoming. Other programs such as Proficiency Testing, External Quality Assurance, or Peer Groups are traditionally used by laboratories to obtain better information about bias.

The use of peer means to determine bias for the Sigma-metric is also less than ideal. This is another consequence of not having a constituent “true value,” or even an assigned value, for all the controls, and may have led to under-estimating bias and thus resulting in a higher Sigma-metric. However, a review of the Method Decision Charts and Sigma performance indicates that the main driver of the metrics for these methods was imprecision. There was additional “room” on the graphs for increased bias for both methods. We can hypothesize that if assigned values for both control materials had been used consistently, the heightened biases would have impacted both metrics equally.

Finally, since this is an instrument- and method-specific study, no conclusions can be made about the comparability of Technopath and Bio-Rad performance on other instrument platforms. Further studies would be necessary to determine the comparability of these control materials for other diagnostic manufacturers.

Conclusion

Based on Sigma-metric analysis, the Technopath controls provide comparable results to the Bio-Rad controls for the analytes in this study. The Sigma performance can be expected to be comparable, and there is no statistically significant difference in variance between the two controls for most analytes. For the ARCHITECT instrument family, Technopath controls can be substituted for Bio-Rad controls with the expectation of comparable performance.

References

1. ISO 15189, *Medical Laboratories* – Particular requirements for quality and competence. ISO, Geneva, 2007.

2. CLSI EP23-A, Laboratory Quality Control Based on Risk Management. Clinical Laboratory Standards Institute, Wayne PA 2011.

3. G Cooper and T Gillons. Producing Reliable Test Results in the Medical Laboratory: Using a quality system approach and ISO 15189 to assure the Quality of laboratory examination procedures. Bio-Rad Laboratories, Irvine CA.

4. JO Westgard, *Six Sigma Quality Design and Control*, 2nd Edition. Westgard QC, Madison WI 2006.

5. SA Westgard, Quantitating Quality: Best Practices for Estimating the Sigma-metric. Abbott White Paper, 2011. http://international.abbottdiagnostics.com/Your_Lab/Six_Sigma/ Last Accessed 2/21/2014.

6. CLIA Proficiency Testing Criteria. Federal Register 28, 1992;57(40):7002-186. Also listed at http://www.westgard.com/clia.htm Last Accessed 2/21/2014.

7. RCPA Allowable Limits of Performance. Available at http://www.westgard.com/rcpa-australasian-quality-requirements. Last accessed 3/17/14. Also available at http://www.rcpaqap.com.au/wp-content/uploads/2013/06/chempath/Allowable%20Limits%20of%20Performance.pdf Last accessed 3/17/14.

8. Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. "Current databases on biologic variation: pros, cons and progress." *Scand J Clin Lab Invest* 1999;59:491-500. 2014 update located at http://www.westgard.com/biodatabase1.htm Last accessed 3/17/14.

9. RiliBÄK (unofficial English translation) – German guidelines for Quality. https://www.westgard.com/rilibak.htm Last accessed 3/17/14. German original: Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen. http://www.bundesaerztekammer.de/downloads/Rili-BAeK-Labor_092013.pdf Last accessed 3/17/14.

10. Ricos C, Ramon F, Salas A, Buno A, Calafell R, Morancho J, Gutierrez-Bassini G, and Jou JM, Interdisciplinary Expert Committee for Quality Specifications in the Clinical LaboratoryMinimum analytical quality specifications of inter-laboratory comparisons: agreement among Spanish EQAP organizers. Clin Chem Lab Med 2012;50(3):485-461. Also available at http://www.westgard.com/minimum-requirements.htm Last accessed 3/17/14.

11. Viljorn A, Singh DK, Farrinton K, Twomey PJ, Analytical quality goals for 25-vitamin D based on biological variation, *J Clin Lab Analysis* 2011 25:2:130-133.

12. JO Westgard. A method evaluation decision chart (MEDx chart) for judging method performance. *Clin Lab Sci* 1995 Sept-Oct;8(5):277-83.

Comparison of Sigma Performance for Chemistry Controls:

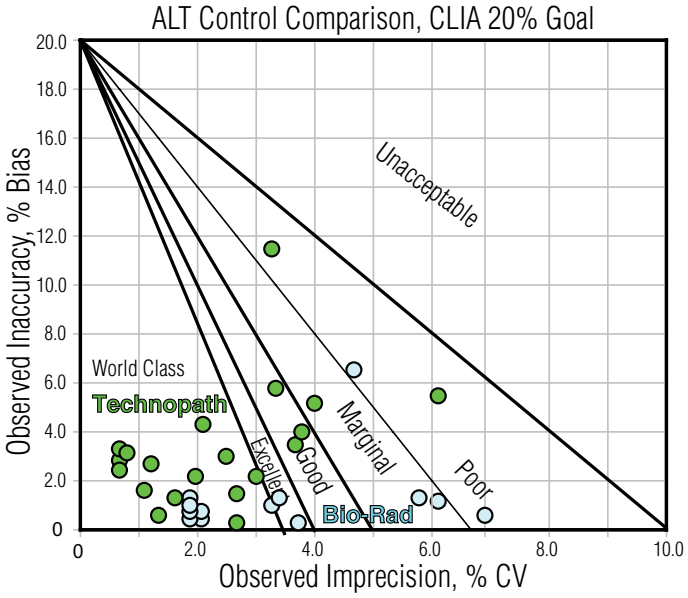

Figure A1. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for ALT.

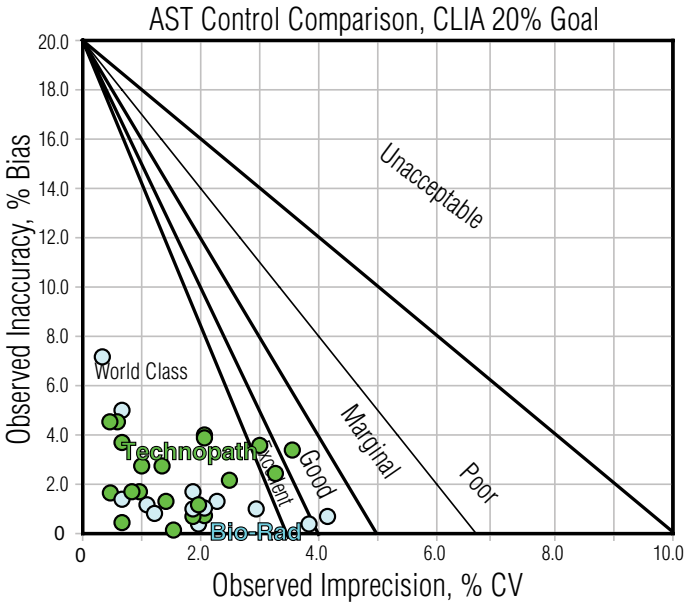

Figure A2. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for AST.

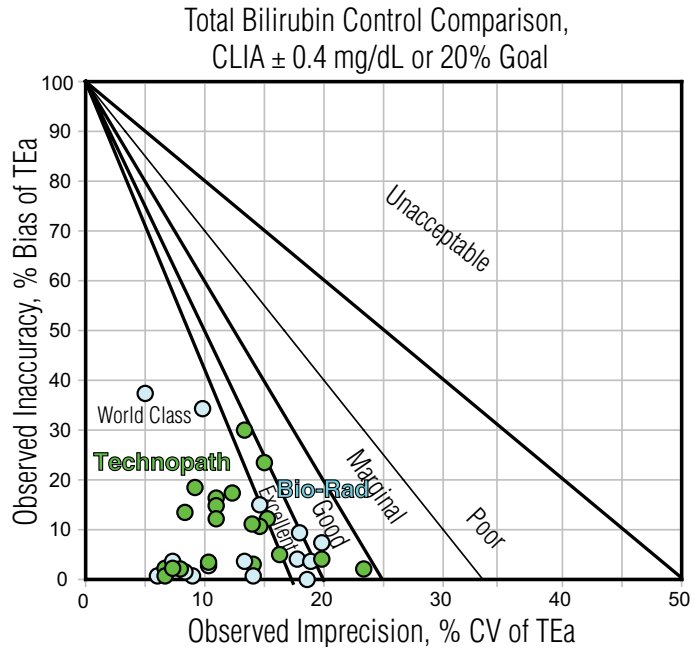

Figure A3. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Total Bilirubin.

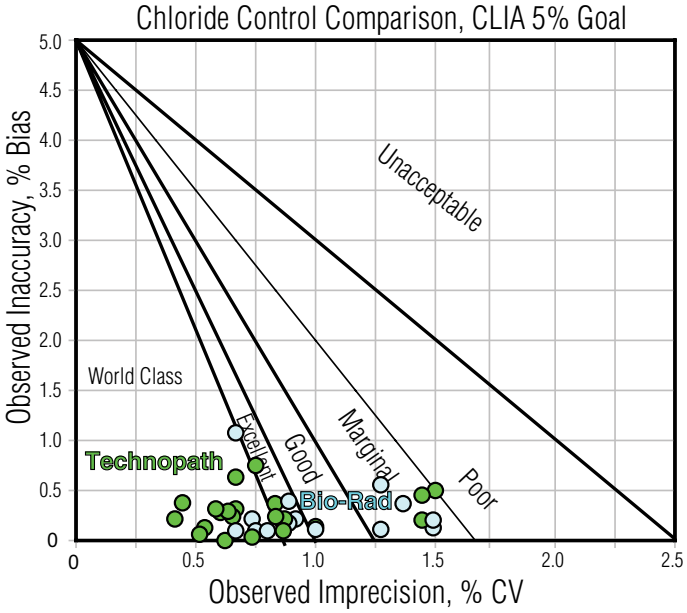

Figure A4. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Chloride.

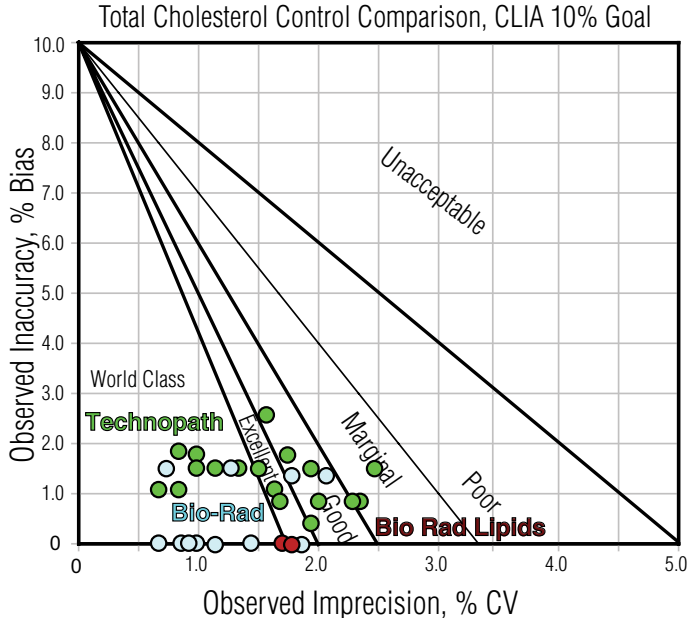

Figure A5. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Total Cholesterol. Data is shown for both Multiqual and Lipids Bio-Rad controls .

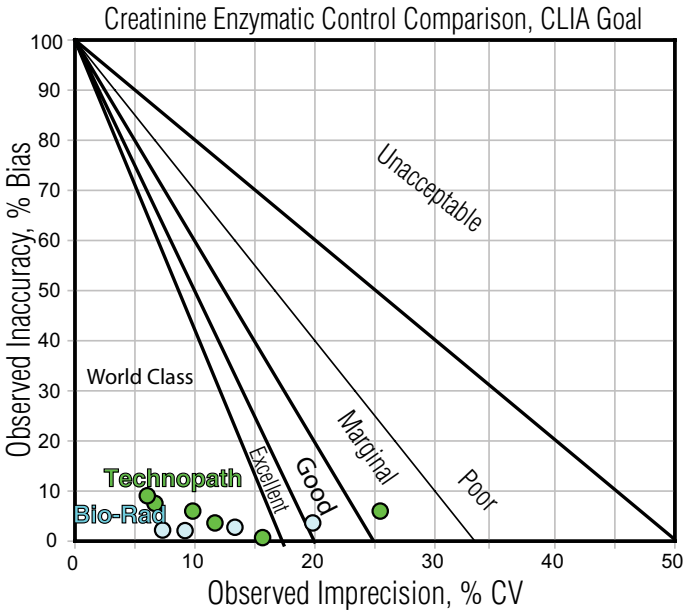

Figure A6. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Creatinine Enzymatic.

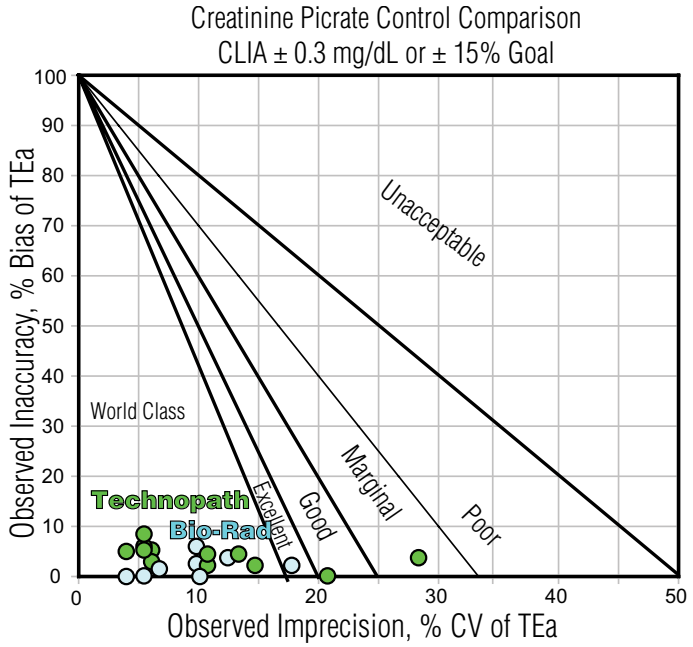

Figure A7. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Creatinine Picrate.

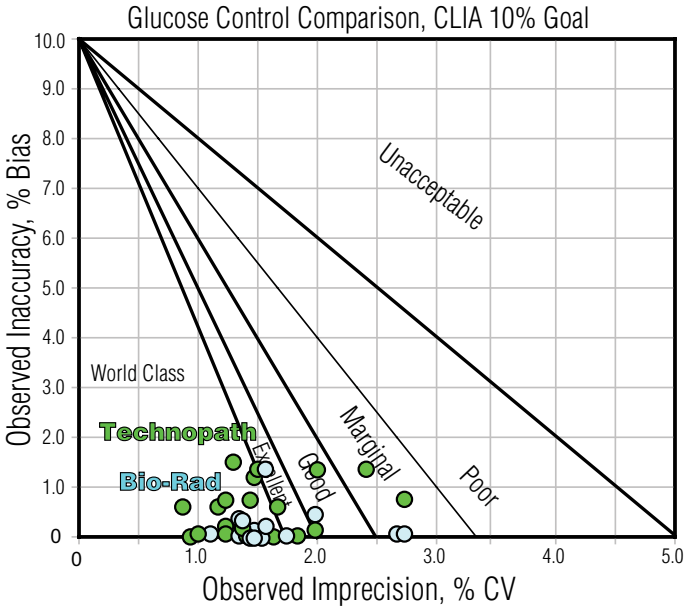

Figure A8. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Glucose.

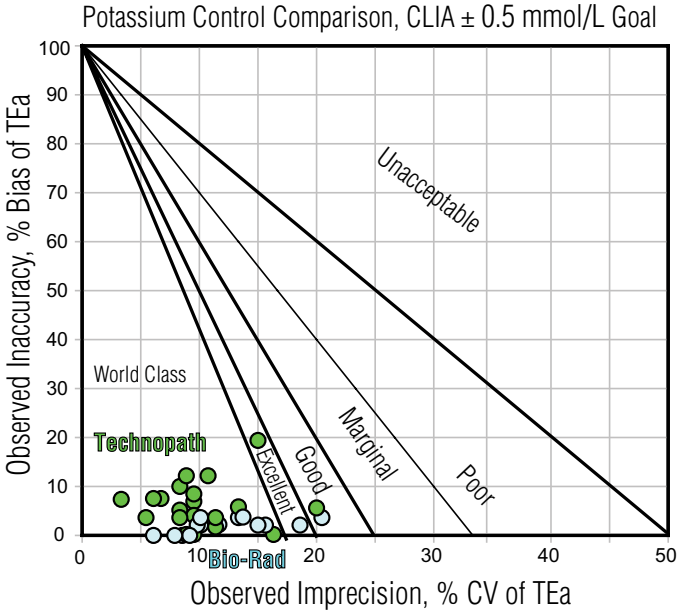

Figure A9. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Potassium.

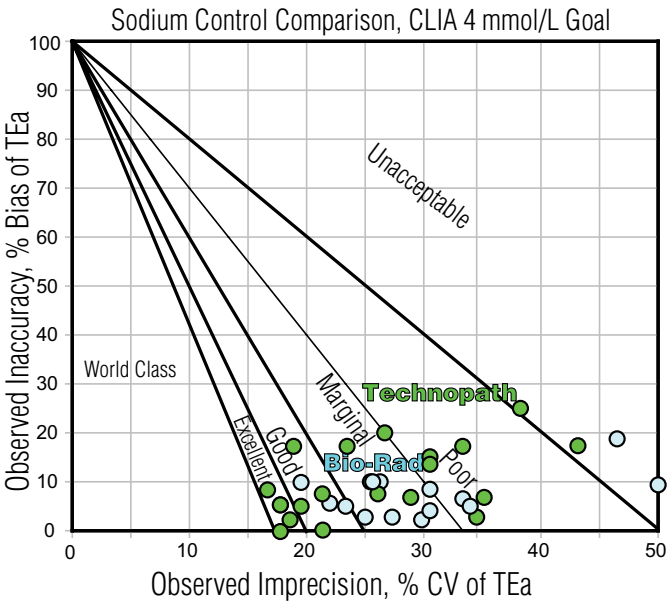

Figure A10. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Sodium.

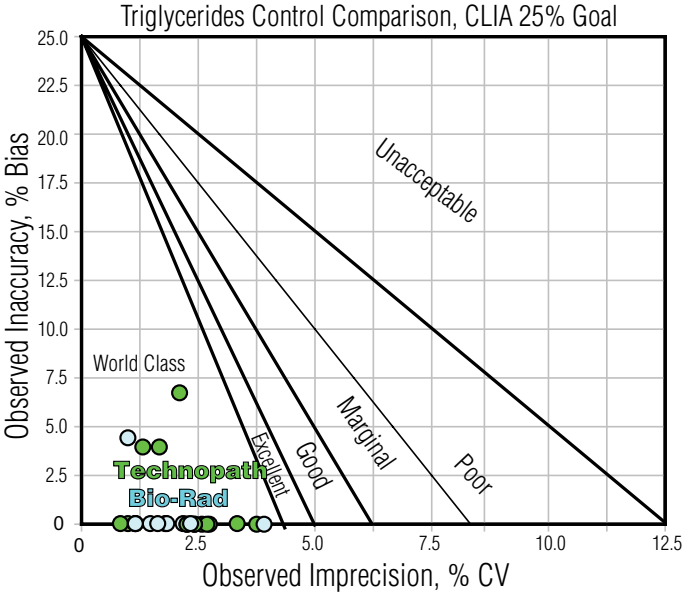

Figure A11. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Triglycerides.

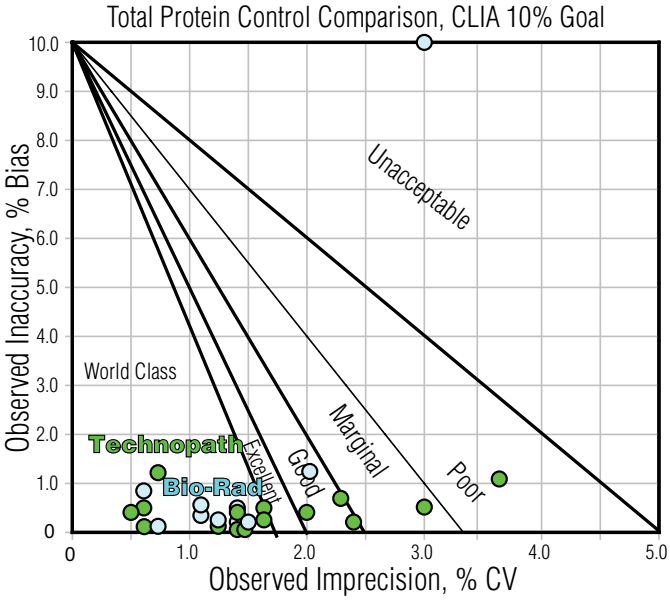

Figure A12. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Total Protein.

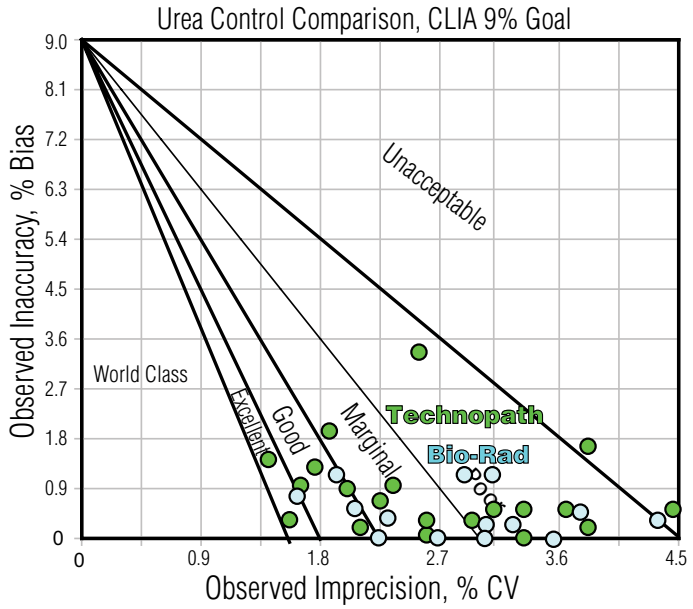

Figure A13. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Urea.

Comparison of Sigma Performance for Urine Controls:

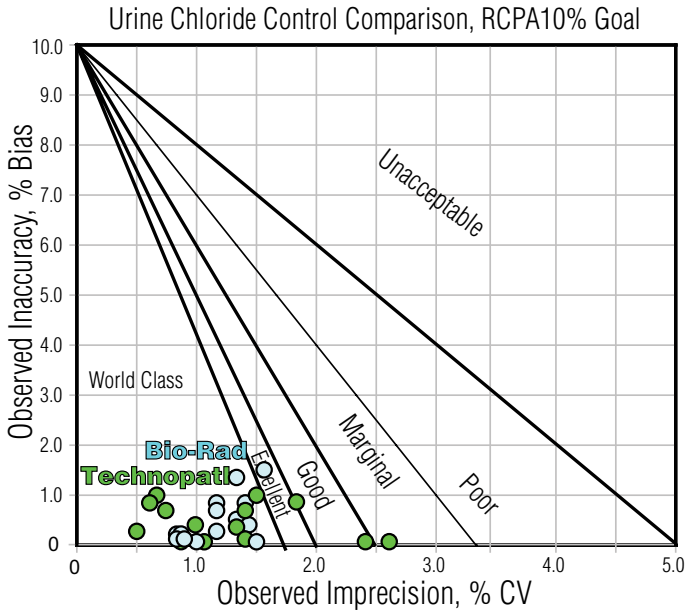

Figure A14. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Urine Chloride.

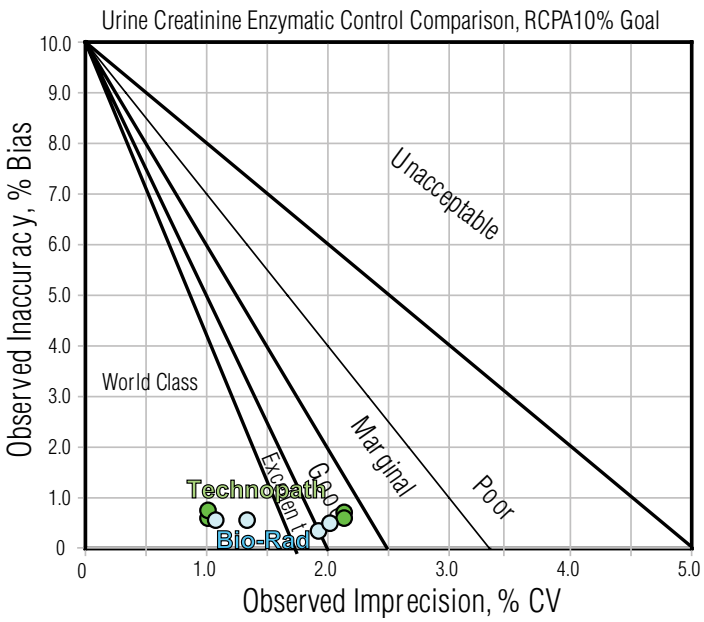

Figure A15. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Urine Creatinine Enzymatic.

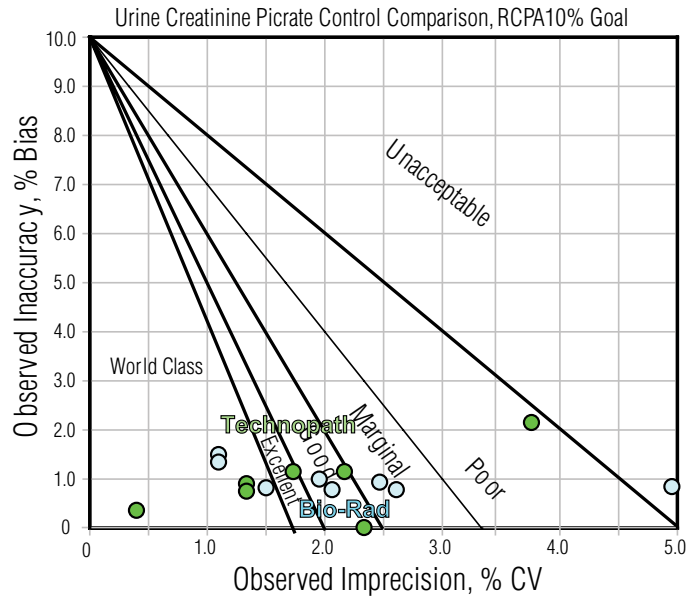

Figure A16. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Urine Creatinine Picrate.

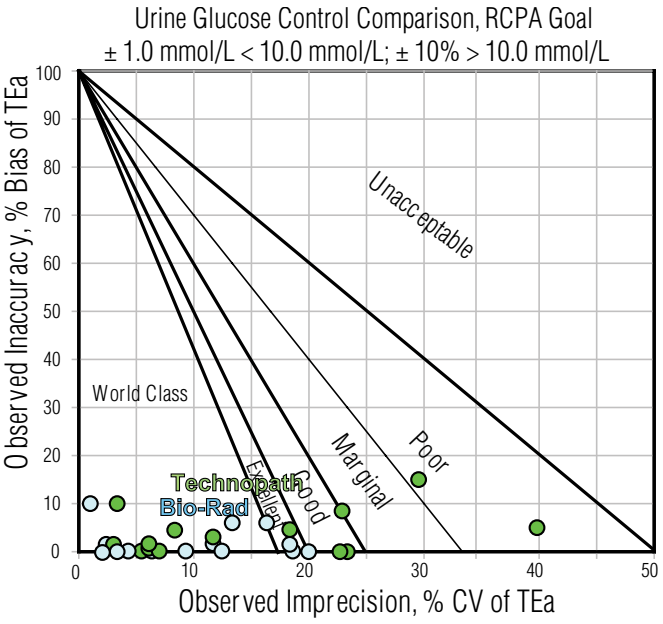

Figure A17. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Urine Glucose.

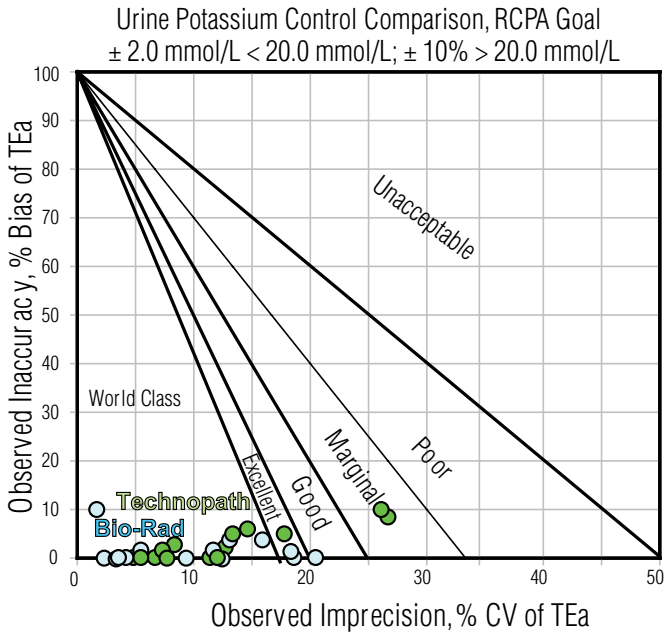

Figure A18. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Urine Potassium.

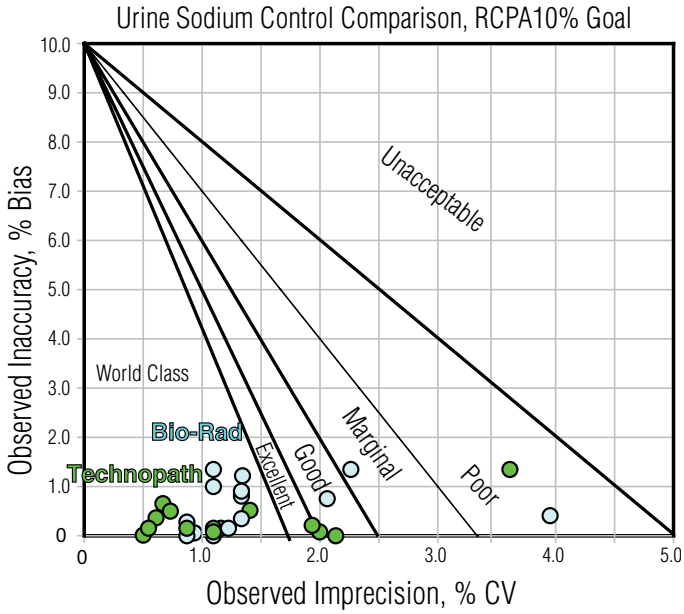

Figure A19. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Urine Sodium.

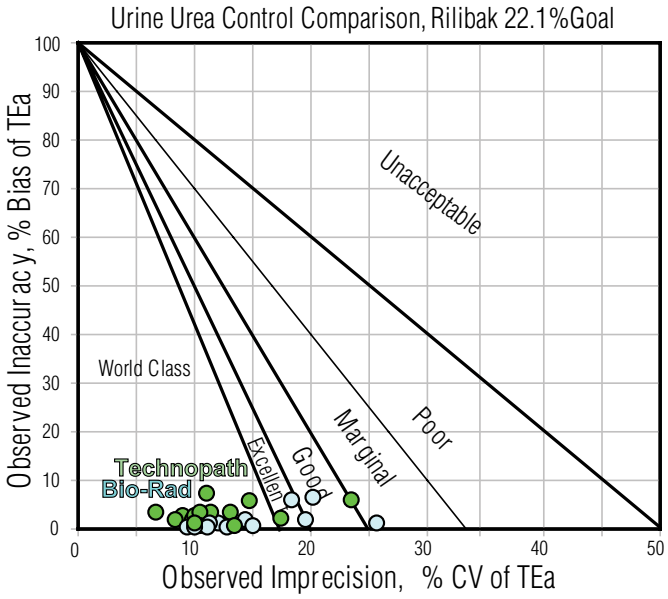

Figure A20. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Urine Urea.

Comparison of Sigma Performance for Immunoassay Controls:

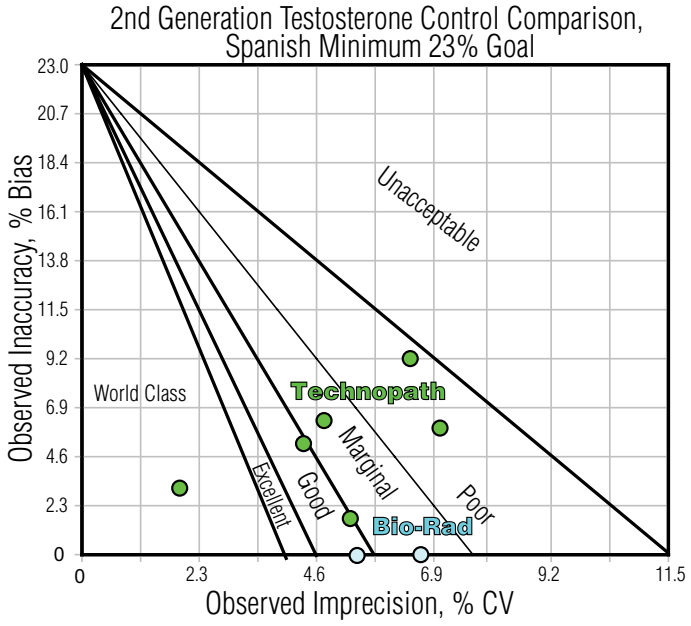

Figure A21. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Second Generation Testosterone. Only two data points for Bio-Rad were available.

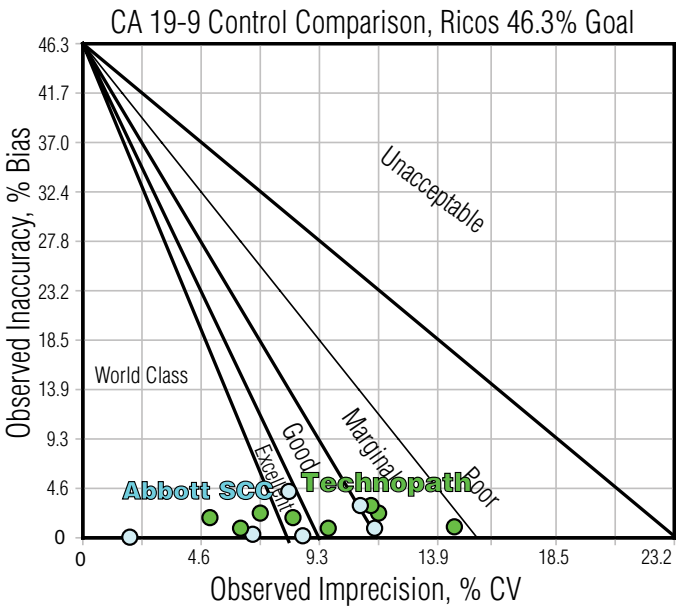

Figure A22. Six Sigma Method Performance comparison of Abbott SCC and Technopath controls for CA 19-9.

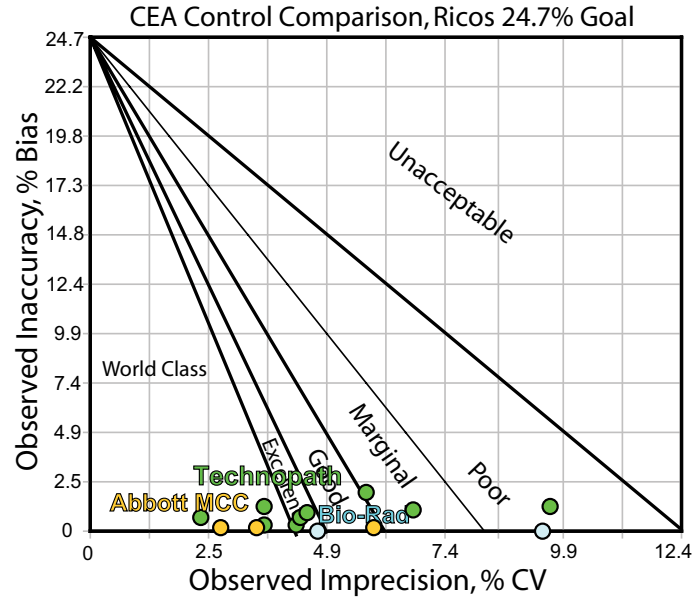

Figure A23. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for CEA. Note that an additional control is displayed here: an Abbott Multi-constitutent control (MCC) which is also produced by Bio-Rad.

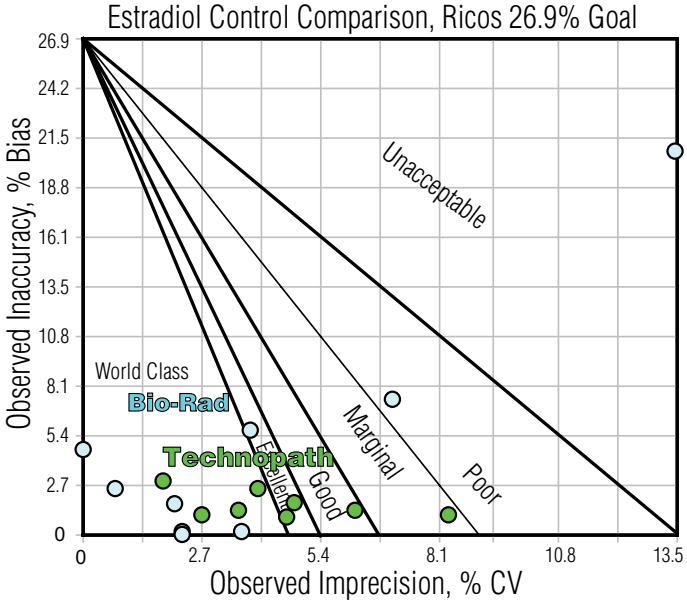

Figure A24. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for Estradiol.

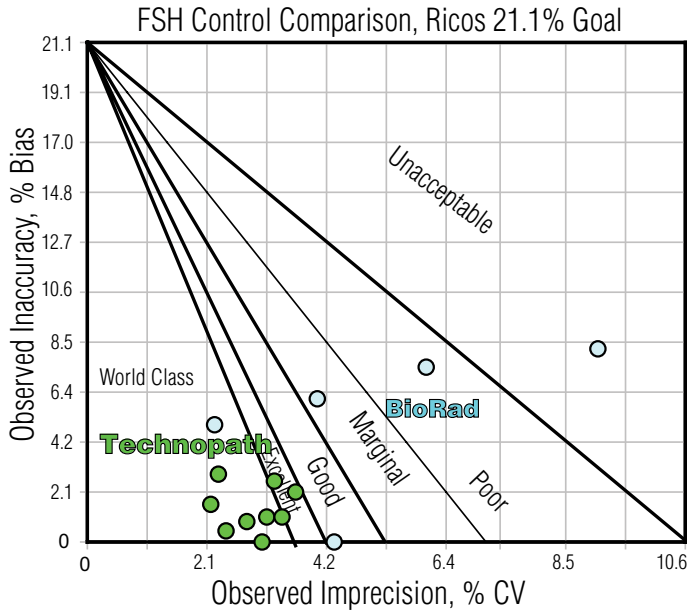

Figure A25. Six Sigma Method Performance comparison of Bio-Rad and Technopath controls for FSH. Fewer data points for Bio-Rad controls were available.

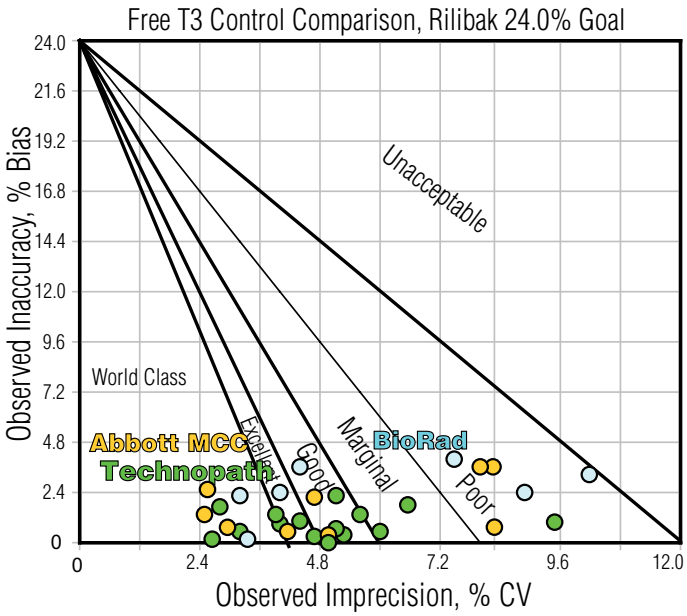

Figure A26. Six Sigma Method Performance comparison of Bio-Rad, MCC (BioRad) and Technopath controls for Free T3.

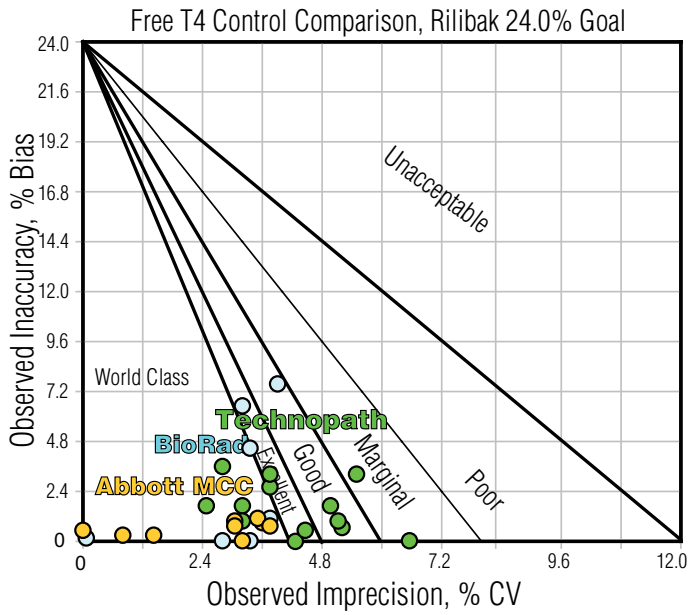

Figure A27. Six Sigma Method Performance comparison of Bio-Rad, MCC (Bio-Rad) and Technopath controls for Free T4.

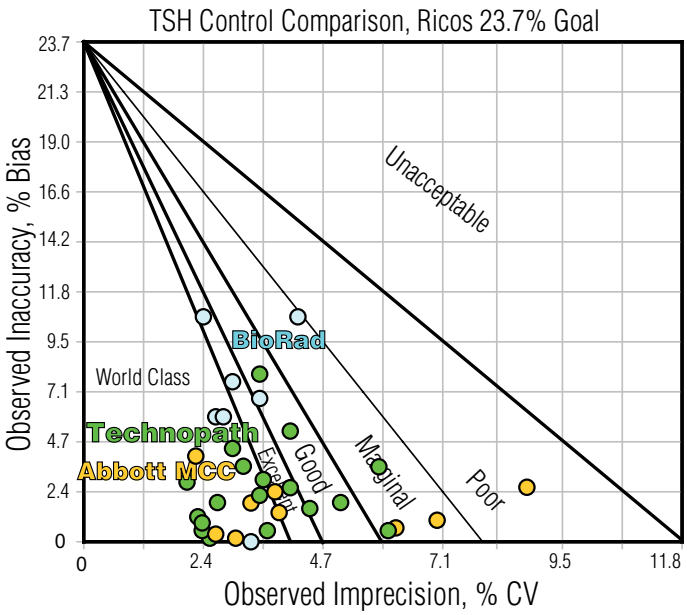

Figure A28. Six Sigma Method Performance comparison of Bio-Rad, MCC (Bio-Rad) and Technopath controls for TSH.

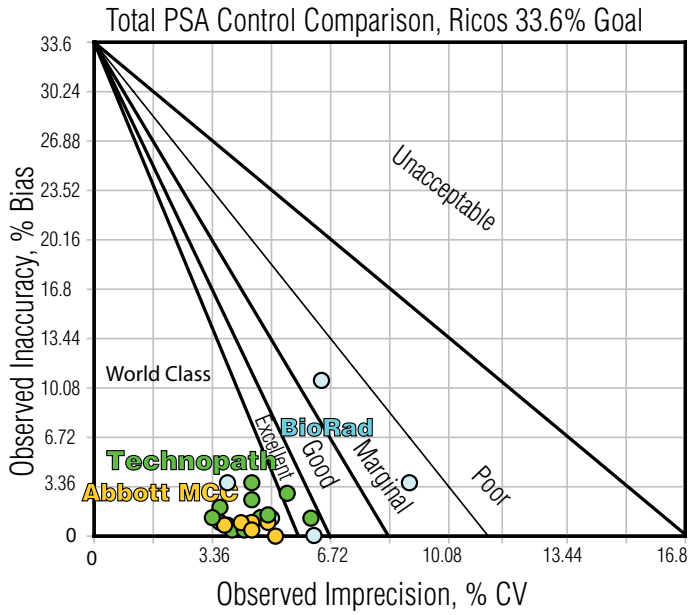

Figure A29. Six Sigma Method Performance comparison of Bio-Rad, MCC (Bio-Rad) and Technopath controls for Total PSA.

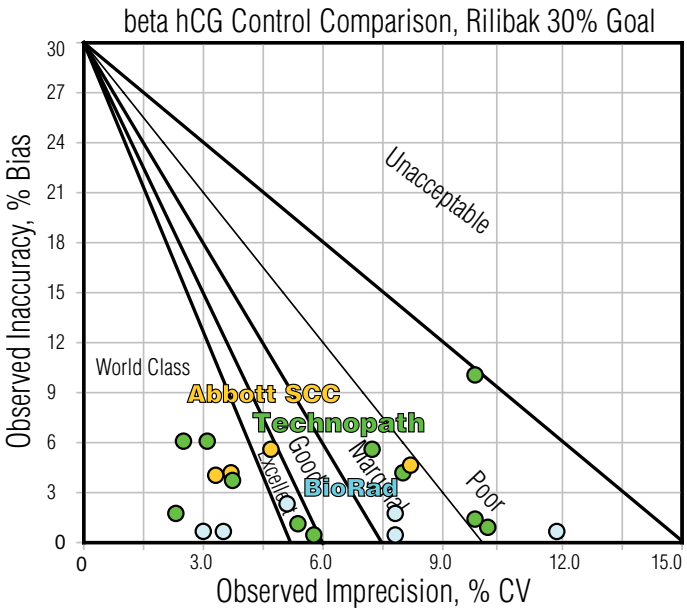

Figure A30. Six Sigma Method Performance comparison of Bio-Rad, Abbott SCC and Technopath controls for beta hCG.

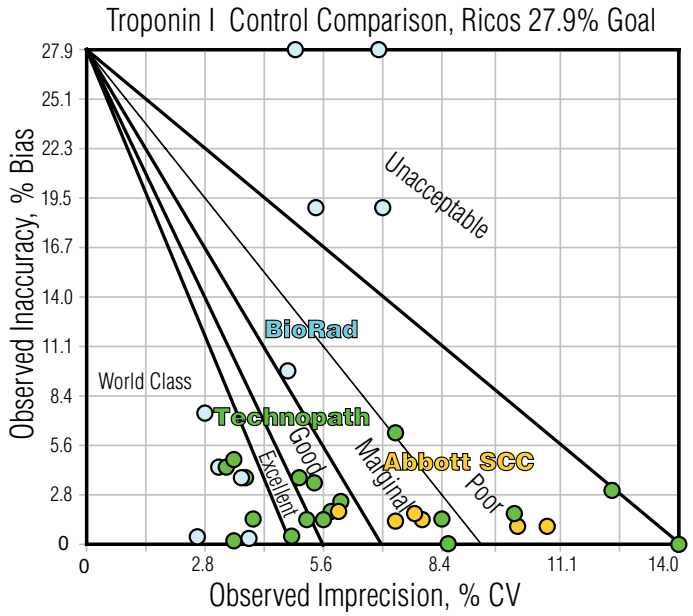

Figure A31. Six Sigma Method Performance comparison of Bio-Rad, Abbott SCC and Technopath controls for Troponin I.

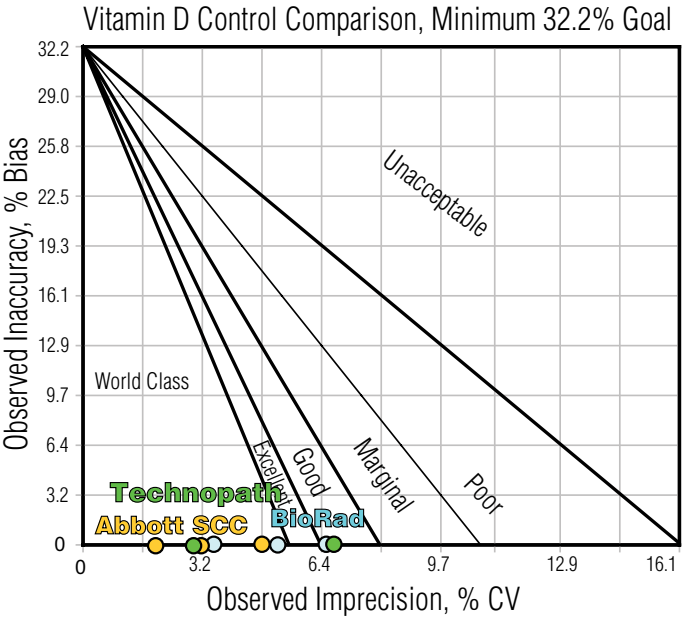

Figure A32. Six Sigma Method Performance comparison of Bio-Rad, Abbott SCC and Technopath controls for Vitamin D.

Abbott
Diagnostics