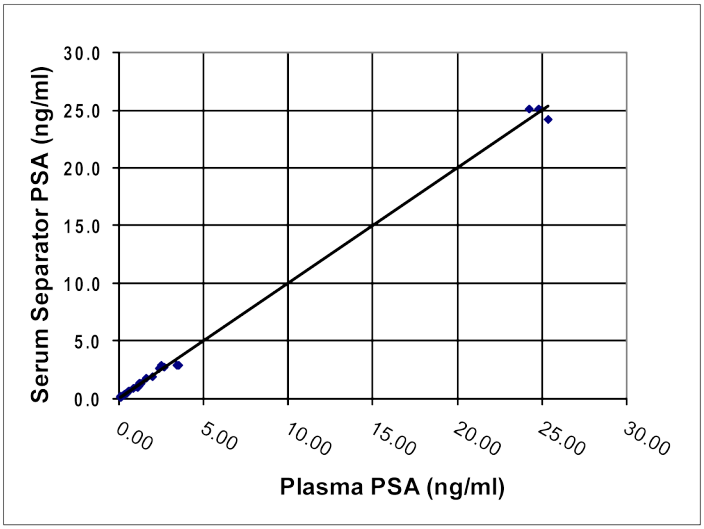
AdvanceDx™ 100
SSE(Serum Separating Extraction) Technology

Technical Bulletin

Prostate Specific Antigen (PSA) Performance Characteristics Using the AdvanceDx 100 Serum Collection Card

Whole Blood collected on the AdvanceDx 100 Serum collection card paired with serum collected by venipuncture were assayed on the ADVIA Centaur Analyzer. The amount of Prostate Specific Antigen in ng/mL was plotted and the paired concentrations were compared using linear regression analysis.



Correlation Coefficient (R)	0.9993
Slope	0.9988
Intercept	0.0193

The AdvanceDx 100 collection card is intended for screening purposes for various clinically significant abnormal analytes. This Technical Bulletin pertains to whole blood using the AdvanceDx 100 collection card followed by laboratory testing of Prostate Specific Antigen.

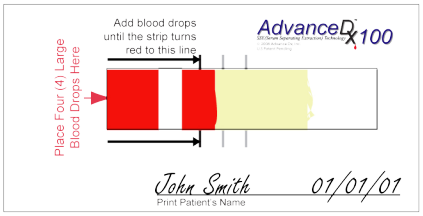
A Prostate Specific Antigen (PSA) test measures the amount of prostate-specific antigen in the blood. PSA is released into a man's blood by his prostate gland. The amount of PSA in the blood normally increases as a man's prostate enlarges with age. PSA may increase as a result of an injury, a digital rectal exam, sexual activity (ejaculation), inflammation of the prostate gland (prostatitis), or prostate cancer.

Reportable Range
When used correctly, the AdvanceDx 100 collection card for Prostate Specific Antigen (PSA) allows for detection of low concentrations down to 0.6 ng/mL or as high as 100 ng/mL.

Reference Range
0 – 4.0 ng/mL

The assay is unaffected by icterus (bilirubin <428 µmol/L or <25 mg/dL), hemolysis (Hb <0.25 mmol/L or <0.4 g/dL), lipemia (Intralipid <1500 mg/dL), and biotin <246 nmol/L or <60 ng/mL.

Specimen Requirements
The AdvanceDx 100 collection card requires approximately four (4) drops of capillary blood placed in the clearly marked application point on the collection card. Blood is placed until the red blood cells reach an easy to read mark identified on the card. The card is air dried and then placed in an envelope containing a desiccant and mailed back to the laboratory. An illustrated instruction guide is included with each AdvanceDx 100 collection card.



Card Stability
The unused AdvanceDx 100 collection card is stable when kept from extremes in humidity and temperature for greater than 2 years.

Specimen Stability
Whole blood collected on the AdvanceDx 100 collection card is stable for 30 days when stored in the supplied envelope when used for Prostate Specific Antigen analysis.

EP Evaluator

PSA

New Century Diagnostics, Inc.

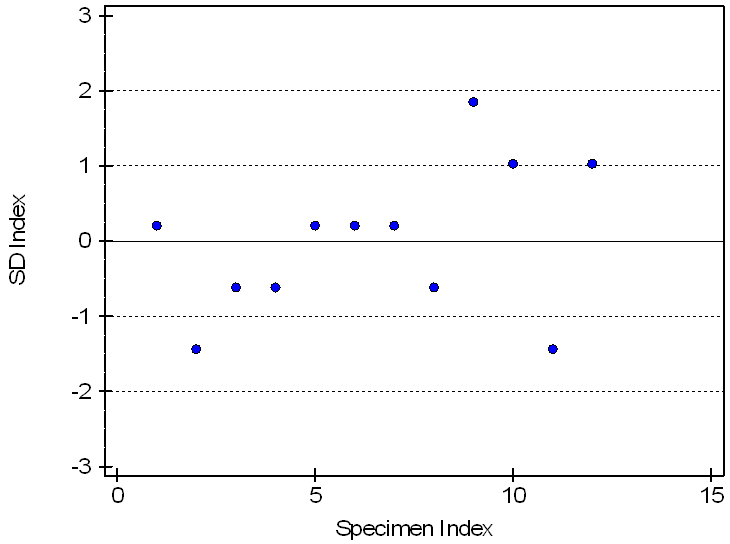
Instrument: Centaur

Sample Name: LOW

Simple Precision

Precision Statistics			
Mean	0.107 ng/ml	95% Confidence for Mean	0.100 to 0.115
Standard Deviation (SD)	0.012	2 SD Range	0.083 to 0.132
95% Confidence for SD	0.009 to 0.021	Number of Specimens (N)	12 of 12
Coefficient of Variation (CV)	11.3%	Number of Outliers	–

Precision Plot



Supporting Data

Analyst:	mp
Expt. Date:	29 Oct 2008
Units:	ng/ml
Screen for Outliers?	No
Comment:	

Precision Data

Index	Results	Index	Results	Index	Results	Index	Results
1	.11	4	.1	7	.11	10	.12
2	.09	5	.11	8	.1	11	.09
3	.1	6	.11	9	.13	12	.12

Accepted by: _____ _____

Signature Date

Simple Precision

Report Interpretation Guide

CLIA and CAP require periodic verification of Precision. The Simple Precision experiment is a quick and dirty way to fulfill the letter of this requirement. The procedure is to make repeated measurements of a single sample, and compute simple statistics like mean, SD, and CV. EP Evaluator offers two additional options:

- Enter a precision goal (Allowable Random Error), and the program will report that the test "passes" if the calculated SD does not exceed Allowable Random Error.
- Automatically identify and remove outliers. (Requires a minimum of 25 results.)

Definitions

Precision: Ability to obtain the same result upon repeated measurement of a specimen. Not necessarily the *correct* result, just the *same* result. (Ability to get the correct result is *Accuracy.)*

Mean: Average value, computed by adding the results and dividing the total by the number of results.

Standard Deviation (SD): The primary measure of dispersion or variation of the individual results about the mean. In other words, a measure of Precision. For many analytes, SD varies with sample concentration. Example: For Glucose, an SD of 10 for a 400 mg/dL sample represents very good precision. For a 40 mg/dL sample, it is very poor precision.

Coefficient of Variation (CV): SD expressed as a percent of the mean. For analytes where error varies with concentration, CV is more likely to remain constant across the analytical range. Example: 2.5% CV for Glucose is very good precision at any concentration.

Within-Run and Total SD: Manufacturers often publish these statistics in package inserts. They are computed from a more complex precision experiment that requires replicate measurements over several days. Total SD from this complex precision experiment is NOT comparable to EP Evaluator's Simple Precision SD.

Number of Specimens (N): A good precision study should include 20-50 replicates. Mathematically, it is possible to calculate SD and CV from only 3 replicates, but it is not a very reliable estimate. For example, suppose the true SD is 1.00. An estimate based on 3 replicates might easily be as low as 0.52 or as high as 6.29 (95% confidence). At N=20, the 95% confidence interval is much narrower: 0.76 to 1.46. At N=50 it narrows further: 0.84 to 1.24.

95% Confidence Interval for SD: In a sense, this measures the "precision of the precision". It show how much the SD might vary if the precision experiment was repeated with different experimental results. The width of the confidence interval depends on two factors: N and the intrinsic SD of the system. The reliability of the precision estimate improves as N increases.

Outlier: A result so far from the others as to arouse suspicion that it was generated by a different mechanism. Some common causes: typing a number with the decimal point in the wrong place, analyzing the wrong sample, or entering incorrect specimen identification.

An outlier can have a drastic effect on the calculated mean and SD. For example:

- Start with 10 results, five 1's and five 2's. The mean is 1.5 and the SD is 0.53
- Change the first 1 to 10. The SD increases from 0.53 to 2.72. The mean changes from 1.5 to 2.4

The best way to deal with an outlier is to (manually) determine its cause and correct it. Another option is to use a statistical procedure, like the one described below, to remove outliers automatically.

Outlier Identification

EP Evaluator identifies outliers using Tukey's method, a nonparametric procedure that is (relatively) unaffected by the outlier it is trying to detect:

- Arrange the results in increasing order, and determine the 25th and 75th percentiles (P25 and P75).
- Determine the Interquartile Range (IQR), IQR = P75 - P25.
- Points greater than P75 + 3 IQR or lower than P25 - 3 IQR are considered outliers. This is roughly comparable to mean +/- 5 SD.

Outliers are excluded from precision calculations, and flagged on the Results Listing. If more than 5% of the results are outliers, the report is stamped PRELIMINARY.

Allowable Total Error (TEa), and the Error Budget

TEa states the laboratory's policy for how much error is medically (or administratively) acceptable. Regulatory requirements represent an upper limit. Example: the CLIA limit for Sodium is 4 mmol/L.

Total Error has two major components: **Systematic Error** (synonym Bias) and **Random Error** (synonym Imprecision). The **Error Budget** allocates a fraction of the Allowable Total Error for Systematic Error, and another fraction for Random Error. Establishing an appropriate Error Budget allows the

Simple Precision

Report Interpretation Guide

lab to control accuracy and precision separately, with reasonable confidence that Total Error will also remain in control. Recommended ranges of values are 25-50% for the Systematic Error Budget and 16-25% for the Random Error Budget.

Pass or Fail?

The objective is to determine whether precision is acceptable, so the standard of comparison is Allowable Random Error. The test passes if the computed SD does not exceed Allowable Random Error.

Example: Suppose Allowable Total Error for Sodium is 4 mmol/L, with a Random Error Budget of 25%. Allowable Random Error is 25% x 4 or 1 mmol/L. The precision test passes when the computed SD is at or below 1 mmol/L.

Preliminary Report

The word PRELIMINARY printed diagonally across the report indicates that the data is incomplete, and the report is not acceptable as a final report. Some or all of the statistics may be missing. Causes:

- Less than 3 unexcluded results.
- More than 5% of the results are outliers.

Chart Interpretation

Levey-Jennings Chart: A scatter plot of Standard Deviation Index (SDI) on the Y-axis vs. specimen index on the X-axis. Specimen index reflects the order in which the results were typed into the program. SDI = (Result - mean) / SD.

Precision Goal: This chart appears only when Allowable Random Error is provided. It diagrams the SD and its 95% confidence interval in relation to allowable random error (the goal). The wide bar represents the SD. The fence marks above and below the SD bar show the 95% confidence limits.

- The report calls the test a "pass" if the SD (top of the wide bar) does not exceed the goal. The bar is green if the test passes, or red if it fails.
- If you consider all points within the 95% confidence interval to be statistically identical, you might consider the test at least marginally acceptable if the lower confidence limit does not exceed the goal.
- The ideal situation is when the upper 95% confidence limit does not exceed the goal.

EP Evaluator

PSA

New Century Diagnostics, Inc.

Instrument: Centaur
Sample Name: LOW

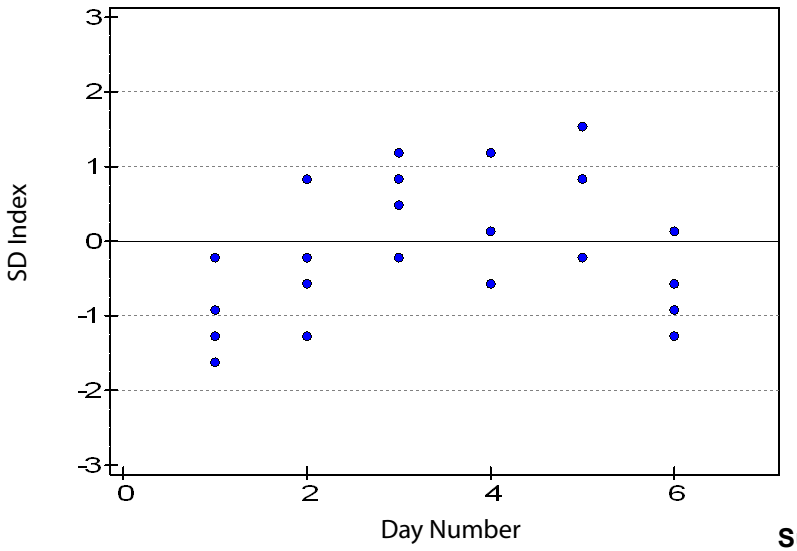
Alternate Precision

Precision Estimate

User's Concentration: 0.136

	Within Run	*Between Run*	*Between Day*	*Total*
Std. Dev	0.021	0.000	0.019	0.028
% CV	15.4	0.0	14.1	20.9
df	18	–	–	13

Precision Plot



Outlier Rejection Criteria

SD	0.012 (calculated)
Multiplier	5.5
Max difference between duplicates	0.066

Preliminary estimate of precision

Mean	0.107	CV	11.3%
SD	0.012	N	12

Results:

.11	.09	.10	.10	.11
.11	.11	.10	.13	.12
.09	.12			

Upper 95% tolerance limit for 95% of user estimates

df for user's experiment	within run SD	total SD
10	0.028	0.038
20	0.026	0.036
30	0.025	0.034
40	0.025	0.034
50	0.024	0.033
60	0.024	0.033
70	0.024	0.032
80	0.024	0.032
90	0.024	0.032
100	0.023	0.032

This table provides data for a manufacturer to include in published materials for users.

Supporting Data

Analyst	mp
Analysis Date	17 Jul 2008 to 17 Dec 2008
Days (total/excl)	6 / 0
Runs per Day	1
Reps per Run	4
Critical Value	95%
Reagent	BioRAD, Lot 40201
Calibrator	SAME, Lot SAME
Units	ng/ml
Verify Mode	Establish Claim
Allowable Total Error	--
Random Error Budget	--
Allowable Rand Error	--
Comment	

Accepted by: _____ _____

Signature Date

Alternate Precision

Experimental Results

	Date	Run	Results				Mean	SD	%CV
1.	17 Jul 2008	1	.1	.13	.09	.11	0.107	0.017	15.9%
2.	22 Jul 2008	1	.16	.12	.10	.13	0.128	0.025	19.6%
3.	31 Jul 2008	1	.15	.16	.17	.13	0.152	0.017	11.2%
4.	06 Aug 2008	1	.17	.12	.17	.14	0.150	0.024	16.3%
5.	10 Oct 2008	1	.16	.18	.13	.18	0.162	0.024	14.5%
6.	17 Dec 2008	1	.14	.11	.12	.10	0.117	0.017	14.5%

'X' indicates an excluded run, 'O' indicates an outlier run, and 'S' indicates a day that does not have a full complement of results. In all of these cases, the entire day is excluded from the calculations.

Complex Precision

Report Interpretation Guide

The Complex Precision Module is used in three situations:

- A manufacturer wants a statistically rugged procedure recognized in the industry to determine precision to be included in official documents for submission to regulatory bodies.
- A user wants to determine whether an instrument meets the manufacturer's claim for precision using a statistically valid approach.
- A user wants to determine both within-run and total precision.

Experiment Procedure

- Define the number of replicates per run, runs per day, and number of days for the experiment. CLSI EP5 recommends 2 replicates per run, 1 or 2 runs per day, for a minimum of 20 days.
- Collect data for a preliminary run of 8-20 results. The preliminary run is used to detect outliers. This step is optional, but strongly recommended. (It is required for EP5 compliance.)
- Collect data for the full duration of the experiment. The number of replicates per run and runs per day must be the same for all days.

Definitions

Precision. Ability to obtain the same result upon repeated measurement of a specimen.

User's Concentration. Grand mean, computed by adding the results (across all days, replicates, and runs) and dividing the total by the number of results.

Claim Concentration. Concentration at which the manufacturer's SD claims were determined. Laboratorians often think of precision in terms of CV, which is somewhat constant across concentrations. However, the statistical calculations in this module are intended to verify SD. Thus the sample tested should be at approximately the manufacturer's claim concentration.

Standard Deviation (SD). SD is the primary measure of Precision (variation of the individual results about the mean). The point of the Complex Precision experiment is either 1) to determine whether the SD meets the manufacturer's claim, or 2) to compute within-run and total SDs to establish such a claim.

SD Components: The experimental results are analyzed by a random-effects Analysis of Variance (ANOVA) procedure to partition the SD into separate components. The two components usually cited in precision claims are within-run and total SD. The intent of the following definition of the components is to be intuitive. NOT to be mathematically correct.

- **Within-run SD.** Measures the "average" SD computed over replicates that occur within the same run
- **Between-run SD.** SD computed from the means of the individual runs.
- **Between-day SD.** SD computed from the means of the individual days.
- **Total SD.** Composite of within-run, between-run, and between-day SD. NOT the answer you would get if you computed an ordinary SD on all the data, ignoring replicate number, day number, and run number.

Claim Value (of SD). Two kinds of claims may be verified: Manufacturer's claims and Medical Requirements. A manufacturer will typically provide separate values for within-run and total SD. A medical requirement is for Total SD only.

Verification Value. You can pass the precision test even if your measured SD is greater than the claim, as long as the difference is not statistically significant. The Verification Value is the largest SD that is not significantly different from the claim. It varies with sample size -- the larger the sample, the closer the Verification Value is to the claim value.

The precision test passes if the computed SD does not exceed the Verification Value.

Critical Value. The confidence level on which the Verification Value is based. Normally the Critical Value is 95%. This means that the Verification Value is equivalent to a 95% confidence limit -- the observed SD meets the manufacturer's claim if its lower 95% confidence limit does not exceed the claim value.

Coefficient of Variation (CV). SD expressed as a percent of the mean.

Degrees of Freedom (df). df is like an "effective N" for an SD component. As df gets larger the confidence limit around the computed SD narrows, and the verification value gets closer to the claimed value.

Outlier. A result so far from the others as to arouse suspicion that it was generated by a different mechanism.

Outlier Rejection

The program first calculates the SD of the preliminary run. This preliminary SD is multiplied by a user-defined Multiplier (usually 5.5) to compute the Maximum Acceptable Difference between Replicates. Any run whose range exceeds this maximum is declared an outlier, and the entire

Complex Precision

Report Interpretation Guide

day is excluded from analysis.

Report Labelling

The Report title is "EP5 Precision" if the experiment meets all requirements of the CLSI (NCCLS) EP5 guideline. Specifically:

- Two replicates per run, either one or two runs per day, for at least 20 days.
- Uses a preliminary run of at least 8 results to establish a preliminary SD. Excludes a replicate pair if the difference between the duplicates exceeds 5.5 times this preliminary SD.

Reports that use other numbers of replicates per run, runs per day, or duration are labeled "Alternate Precision".

Pass or Fail?

The Complex Precision experiment "passes" as long as neither the within-run or total SD exceeds its verification value. However, the experiment might warrent further review if more than 5% of the runs were rejected as outliers.

Preliminary Report

The word PRELIMINARY printed diagonally across the report indicates that the data is incomplete, and the report is not acceptable as a final report. Some or all of the statistics may be missing. Causes:

- Less than 3 days.
- Less than 6 runs.

References

1. Clinical and Laboratory Standards Institute. *Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline.* NCCLS Document EP5-A (1992). CLSI Wayne, PA.

EP Evaluator

PSA

New Century Diagnostics, Inc.

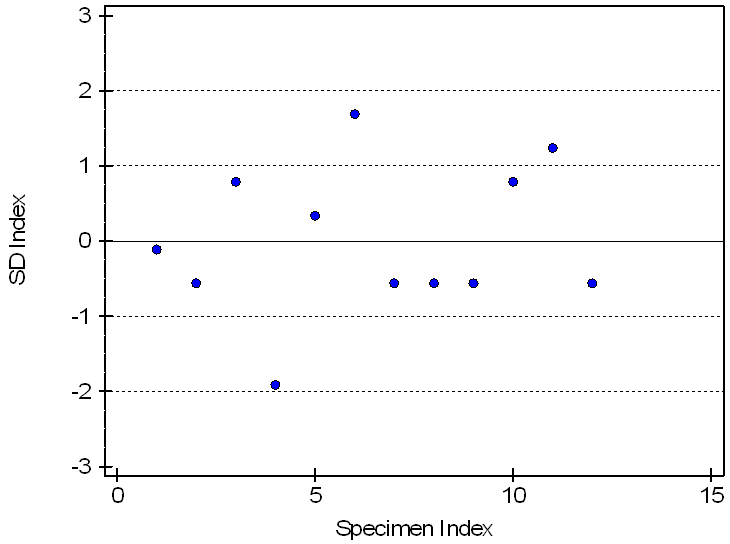
Instrument: Centaur

Sample Name: Med

Simple Precision

Precision Statistics			
Mean	0.243 ng/ml	95% Confidence for Mean	0.228 to 0.257
Standard Deviation (SD)	0.022	2 SD Range	0.198 to 0.287
95% Confidence for SD	0.016 to 0.038	Number of Specimens (N)	12 of 12
Coefficient of Variation (CV)	9.2%	Number of Outliers	–

Precision Plot



Supporting Data

Analyst:	mp
Expt. Date:	29 Oct 2008
Units:	ng/ml
Screen for Outliers?	No
Comment:	

Precision Data

Index	Results	Index	Results	Index	Results	Index	Results
1	.24	4	.20	7	.23	10	.26
2	.23	5	.25	8	.23	11	.27
3	.26	6	.28	9	.23	12	.23

Accepted by: _____ _____

Signature Date

Simple Precision

Report Interpretation Guide

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The best way to deal with an outlier is to (manually) determine its cause and correct it. Another option is to use a statistical procedure, like the one described below, to remove outliers automatically.

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Simple Precision

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Example: Suppose Allowable Total Error for Sodium is 4 mmol/L, with a Random Error Budget of 25%. Allowable Random Error is 25% x 4 or 1 mmol/L. The precision test passes when the computed SD is at or below 1 mmol/L.

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- The report calls the test a "pass" if the SD (top of the wide bar) does not exceed the goal. The bar is green if the test passes, or red if it fails.
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- The ideal situation is when the upper 95% confidence limit does not exceed the goal.

EP Evaluator

PSA

New Century Diagnostics, Inc.

Instrument: Centaur

Sample Name: MED

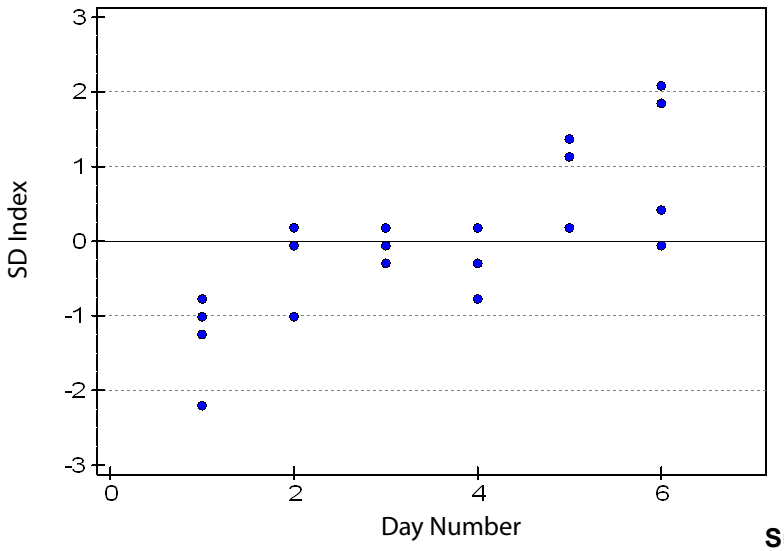
Alternate Precision

Precision Estimate

User's Concentration: 0.323

	Within Run	*Between Run*	*Between Day*	*Total*
Std. Dev	0.027	0.000	0.032	0.042
% CV	8.4	0.0	10.0	13.0
df	18	–	–	10

Precision Plot



Outlier Rejection Criteria

SD	0.019 (calculated)
Multiplier	5.5
Max difference between duplicates	0.1045

Preliminary estimate of precision

Mean	0.246	CV	7.5%
SD	0.019	N	11

Results:

.24	.23	.26	.25	.28
.23	.23	.23	.26	.27
.23				

Upper 95% tolerance limit for 95% of user estimates

df for user's experiment	within run SD	total SD
10	0.036	0.057
20	0.034	0.052
30	0.032	0.050
40	0.032	0.050
50	0.031	0.049
60	0.031	0.048
70	0.031	0.048
80	0.030	0.047
90	0.030	0.047
100	0.030	0.047

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Supporting Data

Analyst	mp
Analysis Date	17 Jul 2008 to 10 Oct 2008
Days (total/excl)	6 / 0
Runs per Day	1
Reps per Run	4
Critical Value	95%
Reagent	BioRAD, Lot 40202
Calibrator	SAME, Lot SAME
Units	ng/ml
Verify Mode	Establish Claim
Allowable Total Error	--
Random Error Budget	--
Allowable Rand Error	--
Comment	

Accepted by: _____ _____

Signature Date

Alternate Precision

Experimental Results

	Date	Run	Results				Mean	SD	%CV
1.	17 Jul 2008	1	.27	.28	.23	.29	0.268	0.026	9.8%
2.	22 Jul 2008	1	.33	.32	.33	.28	0.315	0.024	7.6%
3.	29 Jul 2008	1	.31	.32	.33	.31	0.318	0.010	3.0%
4.	31 Jul 2008	1	.33	.33	.29	.31	0.315	0.019	6.1%
5.	06 Aug 2008	1	.38	.33	.37	.33	0.353	0.026	7.5%
6.	10 Oct 2008	1	.34	.41	.32	.40	0.368	0.044	12.0%

'X' indicates an excluded run, 'O' indicates an outlier run, and 'S' indicates a day that does not have a full complement of results. In all of these cases, the entire day is excluded from the calculations.

Complex Precision

Report Interpretation Guide

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Experiment Procedure

- Define the number of replicates per run, runs per day, and number of days for the experiment. CLSI EP5 recommends 2 replicates per run, 1 or 2 runs per day, for a minimum of 20 days.
- Collect data for a preliminary run of 8-20 results. The preliminary run is used to detect outliers. This step is optional, but strongly recommended. (It is required for EP5 compliance.)
- Collect data for the full duration of the experiment. The number of replicates per run and runs per day must be the same for all days.

Definitions

Precision. Ability to obtain the same result upon repeated measurement of a specimen.

User's Concentration. Grand mean, computed by adding the results (across all days, replicates, and runs) and dividing the total by the number of results.

Claim Concentration. Concentration at which the manufacturer's SD claims were determined. Laboratorians often think of precision in terms of CV, which is somewhat constant across concentrations. However, the statistical calculations in this module are intended to verify SD. Thus the sample tested should be at approximately the manufacturer's claim concentration.

Standard Deviation (SD). SD is the primary measure of Precision (variation of the individual results about the mean). The point of the Complex Precision experiment is either 1) to determine whether the SD meets the manufacturer's claim, or 2) to compute within-run and total SDs to establish such a claim.

SD Components: The experimental results are analyzed by a random-effects Analysis of Variance (ANOVA) procedure to partition the SD into separate components. The two components usually cited in precision claims are within-run and total SD. The intent of the following definition of the components is to be intuitive. NOT to be mathematically correct.

- **Within-run SD.** Measures the "average" SD computed over replicates that occur within the same run
- **Between-run SD.** SD computed from the means of the individual runs.
- **Between-day SD.** SD computed from the means of the individual days.
- **Total SD.** Composite of within-run, between-run, and between-day SD. NOT the answer you would get if you computed an ordinary SD on all the data, ignoring replicate number, day number, and run number.

Claim Value (of SD). Two kinds of claims may be verified: Manufacturer's claims and Medical Requirements. A manufacturer will typically provide separate values for within-run and total SD. A medical requirement is for Total SD only.

Verification Value. You can pass the precision test even if your measured SD is greater than the claim, as long as the difference is not statistically significant. The Verification Value is the largest SD that is not significantly different from the claim. It varies with sample size -- the larger the sample, the closer the Verification Value is to the claim value.

The precision test passes if the computed SD does not exceed the Verification Value.

Critical Value. The confidence level on which the Verification Value is based. Normally the Critical Value is 95%. This means that the Verification Value is equivalent to a 95% confidence limit -- the observed SD meets the manufacturer's claim if its lower 95% confidence limit does not exceed the claim value.

Coefficient of Variation (CV). SD expressed as a percent of the mean.

Degrees of Freedom (df). df is like an "effective N" for an SD component. As df gets larger the confidence limit around the computed SD narrows, and the verification value gets closer to the claimed value.

Outlier. A result so far from the others as to arouse suspicion that it was generated by a different mechanism.

Outlier Rejection

The program first calculates the SD of the preliminary run. This preliminary SD is multiplied by a user-defined Multiplier (usually 5.5) to compute the Maximum Acceptable Difference between Replicates. Any run whose range exceeds this maximum is declared an outlier, and the entire

Complex Precision

Report Interpretation Guide

day is excluded from analysis.

Report Labelling

The Report title is "EP5 Precision" if the experiment meets all requirements of the CLSI (NCCLS) EP5 guideline. Specifically:

- Two replicates per run, either one or two runs per day, for at least 20 days.
- Uses a preliminary run of at least 8 results to establish a preliminary SD. Excludes a replicate pair if the difference between the duplicates exceeds 5.5 times this preliminary SD.

Reports that use other numbers of replicates per run, runs per day, or duration are labeled "Alternate Precision".

Pass or Fail?

The Complex Precision experiment "passes" as long as neither the within-run or total SD exceeds its verification value. However, the experiment might warrent further review if more than 5% of the runs were rejected as outliers.

Preliminary Report

The word PRELIMINARY printed diagonally across the report indicates that the data is incomplete, and the report is not acceptable as a final report. Some or all of the statistics may be missing. Causes:

- Less than 3 days.
- Less than 6 runs.

References

1. Clinical and Laboratory Standards Institute. *Evaluation of Precision Performance of Clinical Chemistry Devices; Approved Guideline.* NCCLS Document EP5-A (1992). CLSI Wayne, PA.

EP Evaluator

PSA

New Century Diagnostics, Inc.

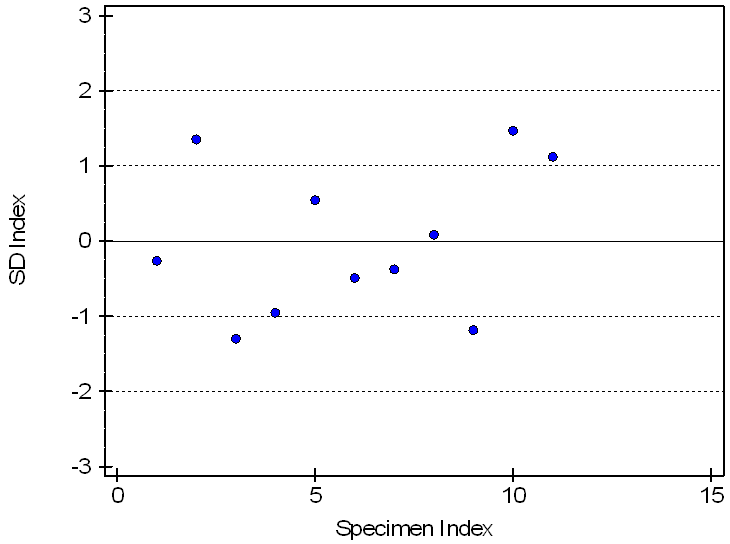
Instrument: Centaur

Sample Name: High

Simple Precision

Precision Statistics			
Mean	1.393 ng/ml	95% Confidence for Mean	1.334 to 1.451
Standard Deviation (SD)	0.087	2 SD Range	1.219 to 1.566
95% Confidence for SD	0.061 to 0.152	Number of Specimens (N)	11 of 11
Coefficient of Variation (CV)	6.2%	Number of Outliers	–

Precision Plot



Supporting Data

Analyst:	mp
Expt. Date:	29 Oct 2008
Units:	ng/ml
Screen for Outliers?	No
Comment:	

Precision Data

Index	Results	Index	Results	Index	Results	Index	Results
1	1.37	4	1.31	7	1.36	10	1.52
2	1.51	5	1.44	8	1.40	11	1.49
3	1.28	6	1.35	9	1.29		

Accepted by: _____ _____

Signature Date

Simple Precision

Report Interpretation Guide

CLIA and CAP require periodic verification of Precision. The Simple Precision experiment is a quick and dirty way to fulfill the letter of this requirement. The procedure is to make repeated measurements of a single sample, and compute simple statistics like mean, SD, and CV. EP Evaluator offers two additional options:

- Enter a precision goal (Allowable Random Error), and the program will report that the test "passes" if the calculated SD does not exceed Allowable Random Error.
- Automatically identify and remove outliers. (Requires a minimum of 25 results.)

Definitions

Precision: Ability to obtain the same result upon repeated measurement of a specimen. Not necessarily the *correct* result, just the *same* result. (Ability to get the correct result is *Accuracy.)*

Mean: Average value, computed by adding the results and dividing the total by the number of results.

Standard Deviation (SD): The primary measure of dispersion or variation of the individual results about the mean. In other words, a measure of Precision. For many analytes, SD varies with sample concentration. Example: For Glucose, an SD of 10 for a 400 mg/dL sample represents very good precision. For a 40 mg/dL sample, it is very poor precision.

Coefficient of Variation (CV): SD expressed as a percent of the mean. For analytes where error varies with concentration, CV is more likely to remain constant across the analytical range. Example: 2.5% CV for Glucose is very good precision at any concentration.

Within-Run and Total SD: Manufacturers often publish these statistics in package inserts. They are computed from a more complex precision experiment that requires replicate measurements over several days. Total SD from this complex precision experiment is NOT comparable to EP Evaluator's Simple Precision SD.

Number of Specimens (N): A good precision study should include 20-50 replicates. Mathematically, it is possible to calculate SD and CV from only 3 replicates, but it is not a very reliable estimate. For example, suppose the true SD is 1.00. An estimate based on 3 replicates might easily be as low as 0.52 or as high as 6.29 (95% confidence). At N=20, the 95% confidence interval is much narrower: 0.76 to 1.46. At N=50 it narrows further: 0.84 to 1.24.

95% Confidence Interval for SD: In a sense, this measures the "precision of the precision". It show how much the SD might vary if the precision experiment was repeated with different experimental results. The width of the confidence interval depends on two factors: N and the intrinsic SD of the system. The reliability of the precision estimate improves as N increases.

Outlier: A result so far from the others as to arouse suspicion that it was generated by a different mechanism. Some common causes: typing a number with the decimal point in the wrong place, analyzing the wrong sample, or entering incorrect specimen identification.

An outlier can have a drastic effect on the calculated mean and SD. For example:

- Start with 10 results, five 1's and five 2's. The mean is 1.5 and the SD is 0.53
- Change the first 1 to 10. The SD increases from 0.53 to 2.72. The mean changes from 1.5 to 2.4

The best way to deal with an outlier is to (manually) determine its cause and correct it. Another option is to use a statistical procedure, like the one described below, to remove outliers automatically.

Outlier Identification

EP Evaluator identifies outliers using Tukey's method, a nonparametric procedure that is (relatively) unaffected by the outlier it is trying to detect:

- Arrange the results in increasing order, and determine the 25th and 75th percentiles (P25 and P75).
- Determine the Interquartile Range (IQR), IQR = P75 - P25.
- Points greater than P75 + 3 IQR or lower than P25 - 3 IQR are considered outliers. This is roughly comparable to mean +/- 5 SD.

Outliers are excluded from precision calculations, and flagged on the Results Listing. If more than 5% of the results are outliers, the report is stamped PRELIMINARY.

Allowable Total Error (TEa), and the Error Budget

TEa states the laboratory's policy for how much error is medically (or administratively) acceptable. Regulatory requirements represent an upper limit. Example: the CLIA limit for Sodium is 4 mmol/L.

Total Error has two major components: **Systematic Error** (synonym Bias) and **Random Error** (synonym Imprecision). The **Error Budget** allocates a fraction of the Allowable Total Error for Systematic Error, and another fraction for Random Error. Establishing an appropriate Error Budget allows the

Simple Precision

Report Interpretation Guide

lab to control accuracy and precision separately, with reasonable confidence that Total Error will also remain in control. Recommended ranges of values are 25-50% for the Systematic Error Budget and 16-25% for the Random Error Budget.

Pass or Fail?

The objective is to determine whether precision is acceptable, so the standard of comparison is Allowable Random Error. The test passes if the computed SD does not exceed Allowable Random Error.

Example: Suppose Allowable Total Error for Sodium is 4 mmol/L, with a Random Error Budget of 25%. Allowable Random Error is 25% x 4 or 1 mmol/L. The precision test passes when the computed SD is at or below 1 mmol/L.

Preliminary Report

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- Less than 3 unexcluded results.
- More than 5% of the results are outliers.

Chart Interpretation

Levey-Jennings Chart: A scatter plot of Standard Deviation Index (SDI) on the Y-axis vs. specimen index on the X-axis. Specimen index reflects the order in which the results were typed into the program. SDI = (Result - mean) / SD.

Precision Goal: This chart appears only when Allowable Random Error is provided. It diagrams the SD and its 95% confidence interval in relation to allowable random error (the goal). The wide bar represents the SD. The fence marks above and below the SD bar show the 95% confidence limits.

- The report calls the test a "pass" if the SD (top of the wide bar) does not exceed the goal. The bar is green if the test passes, or red if it fails.
- If you consider all points within the 95% confidence interval to be statistically identical, you might consider the test at least marginally acceptable if the lower confidence limit does not exceed the goal.
- The ideal situation is when the upper 95% confidence limit does not exceed the goal.

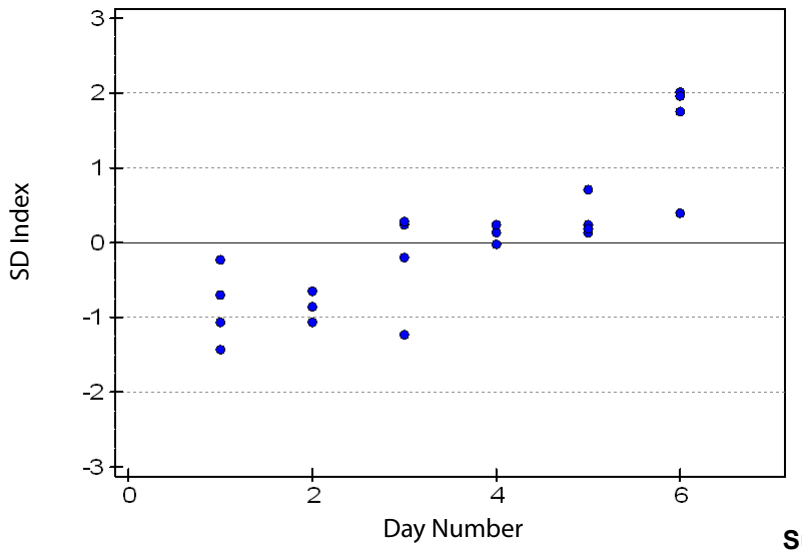
Alternate Precision

Precision Estimate

User's Concentration: 1.7843

	Within Run	*Between Run*	*Between Day*	*Total*
Std. Dev	0.0948	0.0000	0.1664	0.1916
% CV	5.3	0.0	9.3	10.7
df	18	–	–	7

Precision Plot



Outlier Rejection Criteria

SD	0.087 (calculated)
Multiplier	5.5
Max difference between duplicates	0.4785

Preliminary estimate of precision

Mean	1.393	CV	6.2%
SD	0.087	N	11

Results:

1.37	1.51	1.28	1.31	1.44
1.35	1.36	1.40	1.29	1.52
1.49				

Upper 95% tolerance limit for 95% of user estimates

df for user's experiment	within run SD	total SD
10	0.1280	0.2586
20	0.1185	0.2394
30	0.1138	0.2299
40	0.1119	0.2260
50	0.1100	0.2222
60	0.1090	0.2203
70	0.1081	0.2184
80	0.1072	0.2165
90	0.1062	0.2145
100	0.1053	0.2126

This table provides data for a manufacturer to include in published materials for users.

Supporting Data

Analyst	mp
Analysis Date	17 Jul 2008 to 10 Oct 2008
Days (total/excl)	6 / 0
Runs per Day	1
Reps per Run	4
Critical Value	95%
Reagent	BioRAD, Lot 40203
Calibrator	SAME, Lot SAME
Units	ng/ml
Verify Mode	Establish Claim
Allowable Total Error	--
Random Error Budget	--
Allowable Rand Error	--
Comment	

Accepted by: _____ _____

Signature Date

New Century Diagnostics, Inc.

Instrument: Centaur
Sample Name: HIGH

Alternate Precision

Experimental Results

	Date	Run	Results				Mean	SD	%CV
1.	17 Jul 2008	1	1.74	1.58	1.65	1.51	1.6200	0.0983	6.1%
2.	22 Jul 2008	1	1.62	1.66	1.58	1.58	1.6100	0.0383	2.4%
3.	29 Jul 2008	1	1.83	1.746	1.548	1.838	1.7405	0.1349	7.8%
4.	31 Jul 2008	1	1.83	1.78	1.81	1.83	1.8125	0.0236	1.3%
5.	06 Aug 2008	1	1.83	1.81	1.92	1.82	1.8450	0.0507	2.7%
6.	10 Oct 2008	1	1.86	2.17	2.16	2.12	2.0775	0.1466	7.1%

'X' indicates an excluded run, 'O' indicates an outlier run, and 'S' indicates a day that does not have a full complement of results. In all of these cases, the entire day is excluded from the calculations.

Complex Precision

Report Interpretation Guide

The Complex Precision Module is used in three situations:

- A manufacturer wants a statistically rugged procedure recognized in the industry to determine precision to be included in official documents for submission to regulatory bodies.
- A user wants to determine whether an instrument meets the manufacturer's claim for precision using a statistically valid approach.
- A user wants to determine both within-run and total precision.

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Complex Precision

Report Interpretation Guide

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