[redacted]gorithm
[redacted]ation

1. General Descr[redacted]

This specificati[redacted]ns to produce a *Diasensor 2000* calibration vector from acc[redacted]

2. Reference[redacted]

32000-PU01	*Diasen[redacted]*tion, Product Use Procedure
32000-PU01	*Diasensor 2000* Glucose Measurement, Product Use Procedure
32000-PU03	*Diasen[redacted]*itoring, Product Use Procedure
31259-PU01	*Diasensor 2000* Patient Data Analysis, Product Use Procedure
31257-PU01	*Diasensor 2000* Calibration, Product Use Procedure
31257-PU02	*Diasensor 2000* Re-Calibration, Product Use Procedure
31256-PU01	*Diasensor 2000* Evaluation, Product Use Procedure

3. Specifications

3.1 Skin Level Threshold Check

The purpose of the skin level threshold check is to detect an open probe.

For each skin spectrum, perform the Skin Level Threshold Check as follows.

1. Using pixel 7 only, compute normalized floating-point pixel value P_{NORM} in the range [0, 1].
2. If P_{NORM} is in the range [0.3, 0.95], then accept the skin spectra. Otherwise, discard the skin spectra, increment the count of bad skin spectra, and re-collect the skin spectra at the same arm position.
3. If the total bad skin spectra count reaches five (5) in a single session, then reject the entire session.

3.2 Reference Ratio Check

The purpose of the reference ratio check is to detect a dirty probe. In a session, skin spectra are bounded by two reference spectra, denoted by R_1 and R_2 respectively.

Perform the Reference Ratio Check as follows.

1. Collect R_1, the skin spectra, and then R_2.
2. Compute the average pixel values, R_{1AVG} and R_{2AVG} respectively.
3. If the ratio $R_{1AVG} / R_{2AVG} \leq 1.003$ and > 0.997, accept the session. Otherwise, perform the following.
4. Prompt the user to clean the probe and collect R'_2. Discard the original R_2.
5. Compute the average pixel value R_{2AVG}.

6. If the ratio R_{1AVG} / R_{2AVG} < 1.003 and >0.997, accept the session. Otherwise, reject the entire session.

3.3 Standard Deviation Check

Perform the Standard Deviation Check on a set of skin spectra. Let M denote the number of skin spectra in the set. Let S_{ij} denote a particular skin spectra pixel, where i denotes the spectra number {1..M} and j denotes the pixel number {1..64}.

Perform the Standard Deviation Check as follows:

1. Compute standard deviations of individual pixels: σ_j = STDEV (S_{1j}, S_{2j}, ... $S_{M,j}$) for j = 1 to 64.
2. Compute the average of the 64 standard deviations, denoted as σ_{AVG}.
3. If σ_{AVG} < 0.009, accept the sub-session. Otherwise, reject the sub-session.

3.4 PLS Decomposition

3.4.1 Transform the Matrix X_{avg}

The purpose of PLS decomposition is to produce regression coefficients from the mean-centered absorbance spectra and HemoCue readings provided.

Use the bidiagonalization algorithm (see note) to transform the matrix $\mathbf{X}_{avg}$ up to rank p into three matrices, $\mathbf{UBV}^T$, using y_{avg}.

p rank used

m number of channels used + 1 for the invasive glucose value (number of columns)

n number of spectra (number of rows)

X an (n by m) matrix

X_{avg} a matrix that contains mean-centered spectral data **from** the X matrix

y_{avg} a vector containing mean-centered glucose values

rank p the number of factors actually used in the bidiagonalization function

U a (n by p) orthogonal matrix whose columns contain PLS scores, projections into n dimensional space that are themselves derived from the spectra and glucose (X and y matrices, respectively). The PLS scores show normalcy and outliers in spectra.

B a (p by p) diagonal-superdiagonal matrix having nonzero elements on the diagonal and the superdiagonal. the elements demonstrate the magnitude of the PLS scores.

V a (p by m) orthonormal matrix whose columns are the basis vectors of the column space of X_{avg} and whose rows are the loadings, which demonstrate the importance of each column of X_{avg}.

NOTE: Manne, Rolf. "Analysis of Two Partial-Least-Squares Algorithms for Multivariate Calibration." Chemometrics and Intelligent Laboratory Systems. Elsevier Science Publishers. B.V. Amsterdam. 2: 187-197.

3.4.2 The Algorithm for Bidiagonalization

The bidiagonalization algorithm uses the $y_{avg\ vector}$ to transform the matrix X_{avg} for each rank up to p rank into three matrices, UBV. This algorithm is presented below. Some basic terms:

u_j j^{th} PLS Scores or j^{th} column of U.

v_j j^{th} column of V.

q_j pre-normalized v_j

p_j pre-normalized u_j

α_j j^{th} diagonal of B

β_j j^{th} superdiagonal of B

NOTE: *The lower case letters represent a column of a matrix. The subscript represents the particular element.*

The steps of the algorithm follow:

1a. Mean center to get X_{avg} and y_{avg}

1b. Compute the starting vector, $q_1 = X_{avg}^T y_{avg}$ (use to maximize correlation)

1c. Compute $v_1 = q_1 / || q_1 ||$

1d. Compute $p_1 = X_{avg} v_1$

Then, for each rank, 1 through p, compute the following.

2. Compute $u_j = p_j / ||p_j||$

3. Column j of V = v_j Column j of U = u_j

(Builds one column of each matrix, V and U, for each rank)

4. α_j = j th diagonal of **B** = norm of p_j (See **Note**)

(Builds one diagonal of matrix **B** for each rank)

5. $q_{j+1} = u_j^T X_{avg} - \alpha_j v_j$

Perform modified Gram-Schmidt algorithm to insure v_j is orthogonal to the other columns of **V**.

6. β_j = j th superdiagonal of **B** = norm of q_{j+1}

7. Compute $v_{j+1} = q_{j+1} / || q_{j+1} ||$

8. $p_{j+1} = X_{avg} v_{j+1} - \beta_j u_j$

9. Let j = j+1 and go to Step 2.

Stop this procedure when either the norm of $q_j = 0$ or when j is greater than rank p.

Note: *Equations (19) and (20) on page 190 of the Rolf Manne article are equivalent to the ones used here for q_{j+1} and p_{j+1}, but are derived differently. The method used here is as follows.*

$X_{avg} = U B V^T$

$X_{avg} V = U B V^T V$ since we are using an orthonormal basis, $V^T V = I_p$, so

$X_{avg} V = U B$ **(6)**

By fundamental linear algebra, $A e_i$ = the i th column of any matrix **A** and $e_i^T A$ = the i th row of **A**, where **e** is the elementary matrix. This can be applied since it has been established that **B** is a diagonal-superdiagonal matrix. Therefore,

$B e_i = \beta_{i-1} e_{i-1} + \alpha_i e_i$ for $i > 1$ and **(7)**

$e_i^T B = \alpha_i e_i^T + \beta_i e_{i+1}$ for $i \leq n$ **(8)**

Using equations **(7)** and **(8)** to substitute in the decomposition, equations for α_i and β_i can be obtained. The following is the derivation of equations for α_j and β_j, which give the equations for p_{j+1} and q_{j+1}.

α_j	β_j
$X_{avg} V = U B$	$U^T X_{avg} = B V^T$
$X_{avg} V e_i = U B e_i$	$X_{avg}^T U = V B^T$
$X_{avg} V e_i = U (\beta_{i-1} e_{i-1} + \alpha_i e_i)$	$X_{avg}^T U e_i = V B^T e_i$
$X_{avg} V = U \beta_{i-1} e_{i-1} + U \alpha_i e_i^T$	$X_{avg}^T U = V (\alpha_i e_i^T + \beta_i e_{i+1})$
$U \alpha_i e_i = X_{avg} V - U \beta_{i-1} e_{i-1}$	$X_{avg}^T U = V \alpha_i e_i^T + V \beta_i e_{i+1}$
$p_{j+1} = X_{avg} V - U \beta_{i-1} e_{i-1}$ (9)	$V \beta_i e_{i+1} = X_{avg}^T U - V \alpha_i e_i^T$
	$q_{j+1} = X_{avg}^T U - V \alpha_i e_i^T$ (10)

3.5 Glucose Measurement

1. The result of PLS Decomposition is used to calculate a bvector, b; a constant, c; and a normalizing factor, nm.
2. These results are used to calculate a glucose measurement.

   $D2000_i = (nm * (X_i * b)) + c$

   Where X_i is a vector of spectra taken during a particular measurement.

   The normalizing factor is incorporated into the bvector that is used in the Diasensor 2000.

   Therefore, for the embedded software, the formula is essentially:

   $D2000_i = (X_i * b) + c$

3.6 Slope and Intercept Correction (SIC) Calibration Method

1. Perform PLS (rank=53) using the 2880 spectra (approx.) available and obtain the calibration vector.
2. Perform "self-prediction" whereby the calibration spectra are used to obtain $D2000_C$ measurements, which are orthogonally regressed against the corresponding HemoCue values (HQ_C) to obtain the calibration intercept, k_o and the calibration slope, k_1.

   $$D2000_c = k_1 * (HQ_c) + k_0$$

3. Orthogonal Regression is used because both Diasensor 2000 Measurements and HemoCue Measurements are distorted by noise. Orthogonal Regression is presented below.

   The following notations are used to define the slope calculated by Orthogonal Regression:

$$C_{hh} = \sum_{n=1}^{N}\left(h_n - \bar{h}\right)^2$$

$$C_{gg} = \sum_{n=1}^{N}\left(g_n - \bar{g}\right)^2$$

$$C_{hg} = \sum_{n=1}^{N}\left(h_n - \bar{h}\right)\left(g_n - \bar{g}\right)$$

$\bar{h}$ and $\bar{g}$ are average values for HemoCue h_n and measured glucose g_n.

The slope estimate obtained by Orthogonal Regression is defined by the following equation:

$$k_1 = \frac{-(C_{hh} - C_{gg}) + \sqrt{(C_{hh} - C_{gg})^2 + 4\left(C_{hg}\right)^2}}{2C_{hg}}$$

The intercept estimate obtained by Orthogonal Regression is defined by the following equation:

$$k_0 = \bar{g} - k_1 * \bar{h}$$

4. Update the calibration vector using k_0 and k_1 obtained in Step 3. The original calibration vector is divided by $\frac{k_1}{0.9}$, where 0.9 is the correction constant. Then the difference of the original calibration constant and k_0 is divided by $\frac{k_1}{0.9}$.
5. The new calibration vector and constant from Step 4 are then used when calculating a Glucose Measurement.

3.7 Quality Monitoring Cutoff Value (or QM Acceptable Range)

The purpose of the quality monitoring cutoff value is to provide the user with a threshold under which the absolute value of the difference between the *Diasensor 2000* measurement and HemoCue value has to lie for quality control purposes.

Determine the Quality Monitoring Cutoff Value as follows:

For paired Diasensor measurement (x_i) and HemoCue value (y_i) for data collected during calibration, define a root mean square (RMS) error as follows.

$$\mathbf{RMS_{Diasensor}} = \sqrt{\frac{1}{M}\sum_{i=1}^{M}(y_i - x_i)^2}$$ where M is the number of paired results

$$\mathbf{QM\ cutoff\ value} = 2 \cdot \mathbf{RMS_{Diasensor}}$$

3.8 Control Standard Check

The purpose of the control standard check is to identify any gross malfunction of the *Diasensor 2000*.

3.8.1 Calibration

Control standard spectral data is collected during Calibration for each device. At the end of the Calibration period, an 'average' absorbance vector of the control standard data is calculated, as follows:

Convert each control spectrum in a session to absorbance units by using the following equation:[1]

$$\text{absorbance} = \log_{10}\left(\frac{\text{first reference reading}}{\text{control spectrum}}\right)$$

Average all the control absorbance data, by channel, to get the control average absorbance vector.

The control average absorbance vector is sent to the *Diasensor 2000* with the user's Calibration. Both the calibration and the control average absorbance vector are stored in an area that is accessible to the *Diasensor 2000* for future use. During each future sitting where a glucose measurement is calculated, a reading of the control standard is performed. The *Diasensor 2000* then verifies its control status.

3.8.2 Verification that the *Diasensor 2000* is in control

During an Evaluation or Glucose Measurement mode sitting, the current control standard reading is converted to absorbance units. Each channel of the Calibration control average is subtracted from the corresponding channel of the current control data. Then, the minimum difference is subtracted from the maximum difference, as follows:

Max (Current value $_{(1,2,...64)}$ - Average value $_{(1,2,...64)}$) – Min (Current value $_{(1,2,...64)}$ - Average value $_{(1,2,...64)}$)

[1] A Dark spectrum collected at the end of the sitting is subtracted from all spectra in that sitting prior to these calculations and data transfer.

If the maximum difference minus the minimum difference is less than 0.003, the Diasensor is in control. If the maximum difference minus the minimum difference is greater than or equal to 0.003, the Diasensor is out of control and an error message and code are displayed.

3.9 Bias Correction

The Diasensor 2000 when calculating a glucose measurement utilizes bias Correction.

1. Get a raw glucose measurement = $Measurement_{raw}$
2. If this is a Quality Monitoring sitting, do the following:
   a) calculate the new Bias:
      $bias_{new} = Measurement_{raw} - y$
      where
      $Measurement_{raw}$ = The raw preliminary Measurement
      y = The current HemoCue reading
   b) Replace the oldest bias in storage with $bias_{new}$
   c) Calculate the mean of the 5 bias in storage = Correction
   d) Overwrite the old Correction in storage with the new Correction
3. If Quality Monitoring initialization is complete (there are 5 bias' stored), apply the new Correction to the raw measurement to give the glucose measurement:
   Glucose Measurement = $Measurement_{raw}$ - Correction

3.10 Evaluation Pass or Fail Criteria

Calculate the mean of the absolute values of the differences between the paired *HemoCue* and *Diasensor 2000* measurements. Calculate a 95% confidence interval and compare the upper boundary of the confidence interval to a threshold of 90. If the upper boundary is smaller than the threshold of 90, the user is accepted as having passed Evaluation. Otherwise, the user failed Evaluation.

z_α is such that the integral of the standard normal density from $z_{\alpha/2}$ to infinity equals $\alpha/2$.

$\bar{\mu}$ is the estimate of the mean absolute value of the error.

σ is the sample variance.

Assuming that the absolute value of the error is:

$$x_m = |Diasensor - HemoCue|$$

The estimate of the mean absolute value of the error is:

$$\bar{\mu} = \frac{1}{M}\sum_{m=1}^{M}|x_m|$$

The sample standard deviation is:

$$\sigma = \sqrt{\frac{\sum_{m=1}^{M}(x_m)^2 - M(\bar{\mu})^2}{M-1}}$$

The upper boundary of the confidence interval must be less than the threshold of 90 to pass Evaluation:

$$\bar{\mu} + z_{\alpha} \frac{\sigma}{\sqrt{n}} < threshold$$