“Advances Towards the Bionic Pancreas.”

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Renton, WA

DISCLOSURES

Rainier Clinical Research Center is an independent research facility not directly affiliated with any specific drug or device manufacturer, hospital or health care entity.

All funding received from research grants:
Medtronic, Roche, Abbott, Bayer, Senseonics and multiple other device and pharmaceutical manufacturers

Ron Brazg MD, FACE
Rainier Clinical Research Center
“BIONIC”

Utilizing electronic devices and mechanical parts to assist humans in performing difficult, dangerous, or intricate tasks, as by supplementing or duplicating parts of the body.

POTENTIAL BENEFITS OF AN ARTIFICIAL PANCREAS

- Improved glycemic control
- Reduced frequency-severity of hypoglycemia
- Decreased glycemic variability
- Improved quality of life
- Reduced cost:
  - Less frequent ER visits and hospitalizations.
  - Fewer complications
Draft Guidance for Industry and Food and Drug Administration Staff - The Content of Investigational Device Exemption (IDE) and Premarket Applications for Artificial Pancreas Device Systems

DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only. Document issued on: December 6, 2011

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Alternatively, electronic comments may be submitted to http://www.regulations.gov. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this document, contact Charles Zmiki, Ph.D., 301-796-6297, Charles.Zmiki@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

APDS
DIY SYSTEM
COMMERCIAL SYSTEM
SO, WHY IS IT TAKING SO LONG?

500,000 parts and counting........
HISTORICAL PERSPECTIVE

1921
BANTING AND BEST EXTRACT INSULIN

1970
FIRST GLUCOSE METER-AMES CO.

1974
BIOSTATOR-CGM and INSULIN INFUSION

1983*
FIRST INSULIN PUMP AVAILABLE

1991
1st AACE MEETING

1993
DCCT

2004*
CGM FOR PATIENT USE

2016 ??

COMPONENTS OF THE ARTIFICIAL PANCREAS DEVICE SYSTEM (APDS) ("BIONIC PANCREAS")

- Continuous Glucose Sensor
- Blood Glucose Monitoring Device
- Insulin Delivery Device
- Control Algorithm
- Insulin
- + Glucagon, Amylin (Dual Hormone system)
CLOSING THE LOOP

APDS

BGM

INSULIN PUMP

ALGORITHM

CLOSING THE LOOP - BLOOD GLUCOSE MONITOR

APDS

- ADJUNCT TO CGM
- CALIBRATION

BGM

INSULIN PUMP

ALGORITHM

CGM
FACTORS INTERFERING WITH ACCURACY OF SMBG

- Patient characteristics
  - finger cleanliness
  - size of blood sample
  - technique

- Interfering substances
  - maltose, galactose and xylose
  - paracetamol
  - ascorbic acid, uric acid, bilirubin
  - hematocrit

- System accuracy
  - BG meter
  - teststrip variability (lot-lot)

ISO CRITERIA

<table>
<thead>
<tr>
<th></th>
<th>PREVIOUS 2003</th>
<th>CURRENT 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>&lt; 75mg/dl</td>
<td>&lt; 15mg/dl</td>
<td>&lt; 100mg/dl</td>
</tr>
<tr>
<td>&gt; 75mg/dl</td>
<td>&lt; 20%</td>
<td>&gt; 100mg/dl</td>
</tr>
</tbody>
</table>

**ISO** - International Organization for Standardization
Experts share knowledge and develop voluntary, consensus-based, market relevant International Standards
### Results – ISO 15197: 2003

<table>
<thead>
<tr>
<th>SMBG system (reference method)</th>
<th>ISO 15197:2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accu-Chek Aviva Plus (PCA-HK), group 1</td>
<td>Lot 1 % (tests)</td>
</tr>
<tr>
<td>Advocate Redi-Code (YSI)</td>
<td>100% (200/200)</td>
</tr>
<tr>
<td>Embrace (YSI)</td>
<td>96.5% (193/200)</td>
</tr>
<tr>
<td>TRUEbalance (YSI)</td>
<td>96.5% (192/200)</td>
</tr>
<tr>
<td>Accu-Chek Aviva Plus (PCA-HK), group 2</td>
<td>99.0% (198/200)</td>
</tr>
<tr>
<td>WaveSense Presto (YSI)</td>
<td>95.0% (190/200)</td>
</tr>
<tr>
<td>Element (YSI)</td>
<td>97.0% (194/200)</td>
</tr>
<tr>
<td>Prodigy Voice (YSI)</td>
<td>88.5% (177/200)</td>
</tr>
</tbody>
</table>

* Failed to meet current ISO accuracy criteria

Performance Variability of Seven Commonly Used Self-Monitoring of Blood Glucose Systems: Clinical Considerations for Patients and Providers

JDST Vol 7: Jan 2013
Brazg RL, Klaff LJ, Parkin CG

### Results – ISO 15197: 2013

<table>
<thead>
<tr>
<th>SMBG system (reference method)</th>
<th>Proposed ISO (criterion A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accu-Chek Aviva Plus (PCA-HK), group 1</td>
<td>Lot 1 % (tests)</td>
</tr>
<tr>
<td>Advocate Redi-Code (YSI)</td>
<td>100% (200/200)</td>
</tr>
<tr>
<td>Embrace (YSI)</td>
<td>93.0% (183/200)</td>
</tr>
<tr>
<td>TRUEbalance (YSI)</td>
<td>89.5% (174/200)</td>
</tr>
<tr>
<td>Accu-Chek Aviva Plus (PCA-HK), group 2</td>
<td>87.0% (174/200)</td>
</tr>
<tr>
<td>WaveSense Presto (YSI)</td>
<td>87.0% (174/200)</td>
</tr>
<tr>
<td>Element (YSI)</td>
<td>94.0% (182/200)</td>
</tr>
<tr>
<td>Prodigy Voice (YSI)</td>
<td>84.0% (168/200)</td>
</tr>
</tbody>
</table>

* Failed to meet newly proposed ISO accuracy criteria

Performance Variability of Seven Commonly Used Self-Monitoring of Blood Glucose Systems: Clinical Considerations for Patients and Providers

JDST Vol 7: Jan 2013
Brazg RL, Klaff LJ, Parkin CG
BGM PERFORMANCE ASSESSMENT

• GRAPHIC REPRESENTATION
  • Regression Plots
  • Bland-Altman Plots
  • Error Grid Analysis….indicates clinical significance of error
  • Radar Plots

• TABULAR REPRESENTATIONS
  • ISO 15197:2013 guidelines (99% A+B)
  • MAD and MARD......single numeric value
CLOSING THE LOOP - CONTINUOUS GLUCOSE MONITOR

CGM....current status

- **TRANSCUTANEOUS SYSTEMS**
  - Medtronic Enlite
  - Dexcom G4-G5 (nonadjunct use EU)
  - Roche
  - Abbott Navigator, Libre

- **IMPLANTABLE SYSTEMS**
  - Senseonics “Eversense”
  - Eyesense
  - Glysens

- **FLASH GLUCOSE MONITOR** (on demand)
  - Abbott Freestyle Libre (factory calibrated)
HOW ACCURATE DO CGM’s NEED TO BE?

MARD = ?

THE REAL CGM COMPARISON…..

<table>
<thead>
<tr>
<th>Device</th>
<th>MARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAVIGATOR (ABBOTT)</td>
<td>12.4 ± 3.6</td>
</tr>
<tr>
<td>GUARDIAN (MEDTRONIC)</td>
<td>16.4 ± 6.9</td>
</tr>
<tr>
<td>SEVEN PLUS (DEXCOM)</td>
<td>16.7 ± 3.8</td>
</tr>
</tbody>
</table>

Freckmann G, Pleus S et al
SENSOR ACCURACY

Table S6. MARD by FST Day and Glucose Reference Range; Using Sensor Performance Data from the 640G System (640G Pump, Enlite 3 Sensor and G5T3C Transmitter), Abdominal Insertion

<table>
<thead>
<tr>
<th>Reference Range</th>
<th>Characteristic</th>
<th>FST 1</th>
<th>FST 2</th>
<th>FST 3</th>
<th>FST 7</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>A) ≤ 75 mg/dL</td>
<td>N of Paired Points</td>
<td>415</td>
<td>139</td>
<td>139</td>
<td>939</td>
<td>1520</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>12.39 (9.67)</td>
<td>7.55 (5.77)</td>
<td>7.55 (5.77)</td>
<td>7.55 (5.77)</td>
<td>10.55 (8.62)</td>
</tr>
<tr>
<td></td>
<td>Median (SD)</td>
<td>10.54</td>
<td>6.56</td>
<td>6.56</td>
<td>7.05</td>
<td>7.96</td>
</tr>
<tr>
<td></td>
<td>Min. Max.</td>
<td>0.00, 63.14</td>
<td>0.00, 63.14</td>
<td>0.00, 63.14</td>
<td>0.00, 63.14</td>
<td>0.00, 63.14</td>
</tr>
<tr>
<td>B) &gt; 75-180 mg/dL</td>
<td>N of Paired Points</td>
<td>4284</td>
<td>4533</td>
<td>3263</td>
<td>12090</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>13.04 (11.07)</td>
<td>8.93 (7.97)</td>
<td>9.53 (8.97)</td>
<td>9.53 (8.97)</td>
<td>10.53 (8.62)</td>
</tr>
<tr>
<td></td>
<td>Median (SD)</td>
<td>10.22</td>
<td>6.93</td>
<td>6.8</td>
<td>7.84</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Min. Max.</td>
<td>0.00, 63.14</td>
<td>0.00, 63.14</td>
<td>0.00, 63.14</td>
<td>0.00, 63.14</td>
<td>0.00, 63.14</td>
</tr>
<tr>
<td>C) &gt; 180 mg/dL</td>
<td>N of Paired Points</td>
<td>4254</td>
<td>4533</td>
<td>3263</td>
<td>12090</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
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<td>7.84</td>
<td></td>
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<tr>
<td></td>
<td>Min. Max.</td>
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<td>0.00, 63.14</td>
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<td>0.00, 63.14</td>
<td>0.00, 63.14</td>
</tr>
</tbody>
</table>

DEXCOM website....
SENSOR ACCURACY

<table>
<thead>
<tr>
<th>MANUFACTURER</th>
<th>DEVICE</th>
<th>MARD % %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEDTRONIC</td>
<td>GUARDIAN</td>
<td>16</td>
</tr>
<tr>
<td>MEDTRONIC</td>
<td>ENLITE 3 (4th Generation)</td>
<td>9.6 *</td>
</tr>
<tr>
<td>DEXCOM</td>
<td>SEVEN PLUS</td>
<td>16</td>
</tr>
<tr>
<td>DEXCOM</td>
<td>G5</td>
<td>9.0 *</td>
</tr>
<tr>
<td>ABBOTT</td>
<td>FREESTYLE LIBRE FLASH</td>
<td>10.7 *</td>
</tr>
<tr>
<td>ABBOTT</td>
<td>FREESTYLE NAVIGATOR</td>
<td>12.3</td>
</tr>
</tbody>
</table>
Senseonics Continuous Glucose Monitoring System

1. To Initiate A Measurement, Body-Worn Transmitter Sends RF Energy To Subcutaneous Sensor
2. Sensor Sends Raw Data Back To Transmitter, Which Calculates Sensor Glucose
## SENSEONICS .....Sensor Accuracy

<table>
<thead>
<tr>
<th>Site</th>
<th>Sensor to Lab (Clinic Sessions)</th>
<th>Sensor to FS (Home Use)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glucose &gt;75mg/dL MARD (%)</td>
<td>Glucose &lt;75mg/dL MAD (mg/dL)</td>
</tr>
<tr>
<td>Site 1</td>
<td>10.4 (0.6)</td>
<td>6.8 (0.4)</td>
</tr>
<tr>
<td>Site 2</td>
<td>12.8 (0.7)</td>
<td>12.2 (0.7)</td>
</tr>
<tr>
<td>Site 3</td>
<td>11.9 (0.7)</td>
<td>15.0 (1.0)</td>
</tr>
<tr>
<td>Site 4</td>
<td>10.7 (0.6)</td>
<td>13.4 (0.7)</td>
</tr>
<tr>
<td>Site 5</td>
<td>9.9 (0.5)</td>
<td>13.9 (0.7)</td>
</tr>
<tr>
<td>Site 6</td>
<td>12.8 (0.7)</td>
<td>15.6 (0.9)</td>
</tr>
<tr>
<td><strong>Combined Accuracy</strong></td>
<td><strong>11.4 (0.7)</strong></td>
<td><strong>13.5 (0.8)</strong></td>
</tr>
</tbody>
</table>

CE Mark Submission, Primary Effectiveness End Point

90 day MARD(Glucose>75mg/dL)=**11.4%**

## SENSEONICS....Survivability Analysis

![Kaplan-Meier Survival Analysis](image)
HOW ACCURATE DO CGM’s NEED TO BE?

MARD < 10 %

CLOSING THE LOOP – ALGORITHM

APDS

BGM

INSULIN PUMP

CGM

ALGORITHM
DELAYS IN CLOSED LOOP CONTROL

CLOSED LOOP CONTROL ALGORITHMS

- **PID** (Proprtional Integral Derivative) controller
  - rely on meal announcement
- **MPC** (Model Predictive Control)
  - rely on meal announcement
- **GPC** (Generalized Predictive Control)
  - adaptive control
  - no meal or activity announcement
The Iterative Steps to the Automation of Insulin Administration

- Threshold Suspend (LGS)
- Predictive Low Glucose Management (PLGS)
- Predictive Low Suspend + Overnight Closed Loop
- Hybrid Closed Loop.....( IC Ratio, Active Insulin Time)
- Full Closed Loop Artificial Pancreas
  - Insulin only
  - Dual hormone
**The ASPIRE Study**

Assess Low Glucose Suspend feature in the MiniMed Paradigm® Veo System to lower duration and severity of hypoglycemia induced from exercise in 50 subjects.

<table>
<thead>
<tr>
<th></th>
<th>DURATION OF HYPO</th>
<th>NADIR mg/dL</th>
<th>END OBS mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>LGS ON</td>
<td>138.5 min</td>
<td>59.6</td>
<td>91.4</td>
</tr>
<tr>
<td>LGS OFF</td>
<td>170.7 min</td>
<td>57.6</td>
<td>66.2</td>
</tr>
<tr>
<td>p-VALUE</td>
<td>0.006</td>
<td>0.015</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


**PLGM**

Hypoglycemia Prevention and User Acceptance of an Insulin Pump System with Predictive Low Glucose Management

The SmartGuard system suspends insulin delivery if the SG level is predicted to drop below 20 mg/dL (1.1 mmol/L) above the preset low limit within the next 30 min.

Pratik Choudhary, MD,1 Birthe S. Olsen, MD,2 Ignacio Conget, MD,3 John B. Welsh, MD, PhD,4 Linda Vorrink, MSc,5 and John J. Shin, PhD4
CLOSING THE LOOP

“HYBRID CLOSED LOOP”

APDS

BGM

CGM

INSULIN PUMP

ALGORITHM

OPEN LOOP......

AVE SG
191 mg/dl
CLOSING THE LOOP. ......IN HCL 1 WEEK

AVE SG 146 mg/dl

CLOSING THE LOOP.....IN HCL 4 WEEKS

AVE SG 131 mg/dl
PRE HCL.....AVE SG (126-182 mg/dl)

IN HCL.........(AVE SG 143 mg/dl)
IN HCL......(AVE SG 127mg/dl)
FAILURE IS NOT AN OPTION

HISTORICAL PERSPECTIVE

1921
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1st AACE MEETING

1993
DCCT

2016
"HYBRID CLOSED LOOP"

2004*
CGM FOR PATIENT USE

AUTOMATION OF INSULIN DELIVERY

SUMERPLGM..........LGS............................SAP....
BARRIERS TO IMPLEMENTATION OF NEW DIABETES TECHNOLOGY

• The physician and clinical inertia
• Usability and the human interface – training
• Accuracy
• Regulatory approval
• Sensor lifetime
• Calibration frequency
• Assessment of clinical benefit
• Cost and reimbursement

Interview with MedPage Today, Nov 2015
Jill Whitcomb case.

Judge: Medicare Must Cover CGM for T1D Patient
Courts may be forcing CMS' hand for coverage of continuous glucose monitors

• "As far as moving forward, it will take patients themselves, individually and through patient advocacy groups, to pressure their legislators to change the Medicare coverage language to recognize the tangible benefits this technology represents to their constituents' lives," Grunberger said. "The professional societies have done their part in incorporating the technology into their position statements and guidelines."
THANK YOU