"Advances Towards the Bionic Pancreas."

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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

"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

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Draft Guidance for Industry and Food and Drug Administration Staff - The Content of Investigational Device Exemption (IDE) and Premarket Applications for Artificial Pancreas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DRAFT GUIDANCE
This guidance document is being distributed for comment purposes only.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

PDF Printer Version

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be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 Zimliki, Ph.D., 301-796-6297, Charles.Zimliki@fda.hhs.gov.

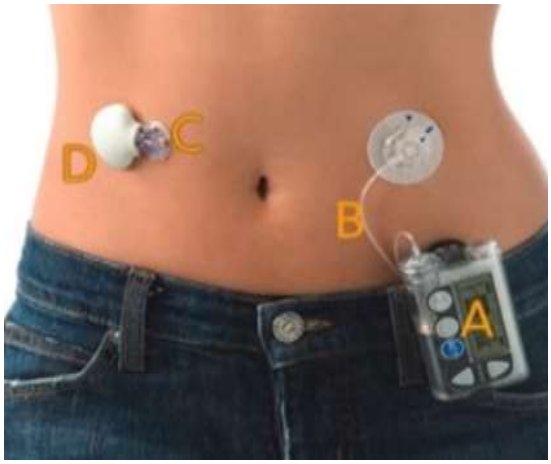
Center for Devices and Radiological Health
CDRH

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

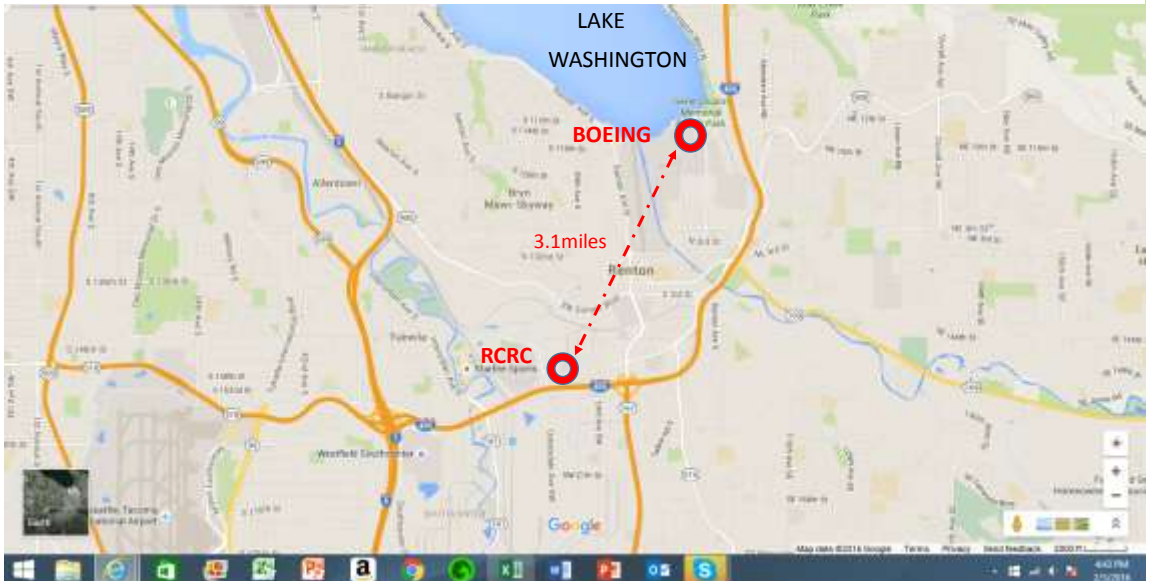
APDS

DIY SYSTEM

COMMERCIAL SYSTEM

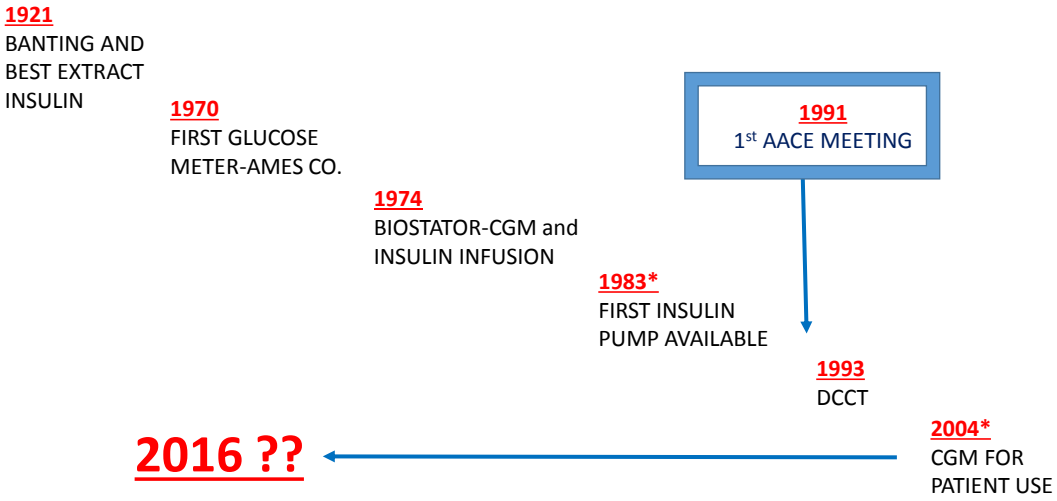


SO, WHY IS IT TAKING SO LONG ?



500,000 parts and counting……

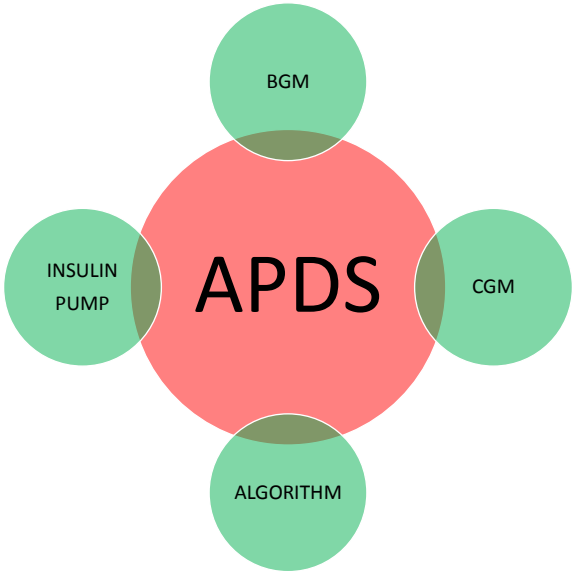
HISTORICAL PERSPECTIVE



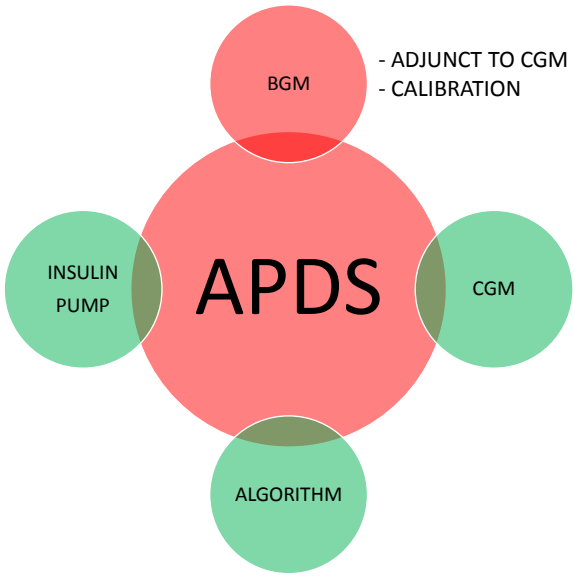
COMPONENTS OF THE ARTIFICIAL PANCREAS DEVICE SYSTEM (APDS) ("BIONIC PANCREAS")

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

CLOSING THE LOOP



CLOSING THE LOOP- BLOOD GLUCOSE MONITOR



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

PREVIOUS 2003		CURRENT 2013	
95%		95%	
< 75mg/dl	< 15mg/dl	< 100mg/dl	< 15mg/dl
> 75mg/dl	< 20%	> 100mg/dl	< 15%

ISO - International Organization for Standardization
Experts share knowledge and develop voluntary, consensus-based, market relevant International Standards

Results – ISO 15197: 2003

SMBG system (reference method)	ISO 15197:2003 Lot 1 % (tests)	Lot 2 % (tests)	Lot 3 % (tests)
Accu-Chek Aviva Plus (PCA-HK), group 1	100% (200/200)	99.5% (199/200)	99.5% (199/200)
Advocate Redi-Code (YSI)	96.5% (193/200)	95.0% (190/200)	**88.5%**[a] (177/200)
Embrace (YSI)	95.0% (190/200)	**93.0%**[a] (186/200)	97.0% (194/200)
TRUEbalance (YSI)	96.0% (192/200)	**91.0%**[a] (182/200)	97.5% (195/200)
Accu-Chek Aviva Plus (PCA-HK), group 2	99.0% (198/200)	99.0% (198/200)	99.0% (198/200)
WaveSense Presto (YSI)	95.0% (190/200)	95.0% (190/200)	97.5% (195/200)
Element (YSI)	97.0% (194/200)	98.0% (196/200)	95.5% (191/200)
Prodigy Voice (YSI)	**88.5%**[a] (177/200)	98.0% (196/200)	95.0% (190/200)

[a] *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

Only **three** of the seven SMBG systems tested met the previous ISO accuracy criteria

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

Results – ISO 15197: 2013

SMBG system (reference method)	Proposed ISO (criterion A) Lot 1 % (tests)	Lot 2 % (tests)	Lot 3 % (tests)
Accu-Chek Aviva Plus (PCA-HK), group 1	100% (200/200)	99.0% (198/200)	98.5% (197/200)
Advocate Redi-Code (YSI)	**93.0%**[a] (186/200)	**86.5%**[a] (173/200)	**84.0%**[a] (168/200)
Embrace (YSI)	**89.5%**[a] (179/200)	**87.0%**[a] (174/200)	**87.5%**[a] (175/200)
TRUEbalance (YSI)	**87.0%**[a] (174/200)	**87.0%**[a] (174/200)	**83.5%**[a] (167/200)
Accu-Chek Aviva Plus (PCA-HK), group 2	97.0% (194/200)	97.5% (195/200)	98.5% (197/200)
WaveSense Presto (YSI)	**87.0%**[a] (174/200)	**88.0%**[a] (176/200)	**85.0%**[a] (170/200)
Element (YSI)	**94.0%**[a] (188/200)	**93.5%**[a] (187/200)	**90.5%**[a] (181/200)
Prodigy Voice (YSI)	**84.0%**[a] (168/200)	96.5% (193/200)	**93.0%**[a] (186/200)

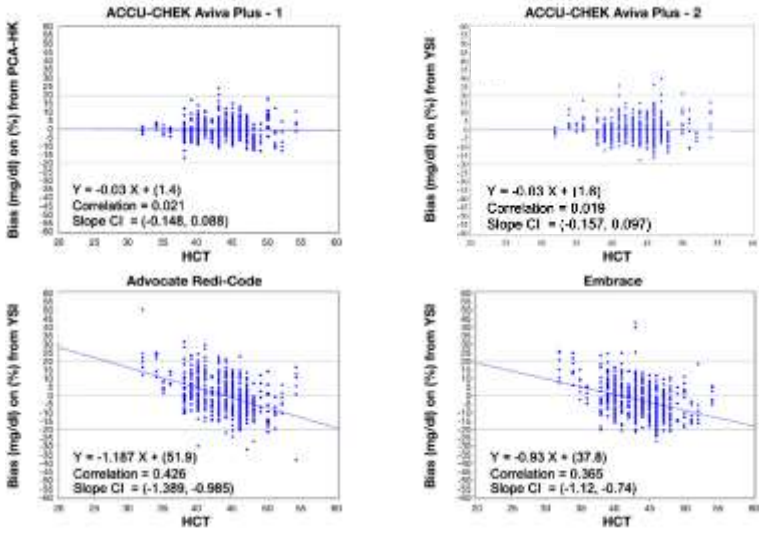
[a] *Failed to meet newly proposed ISO accuracy criteria*

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

Only **one** of the seven SMBG systems tested met the current ISO accuracy criteria

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

BGM Accuracy…….Bias vs. HCT Plots



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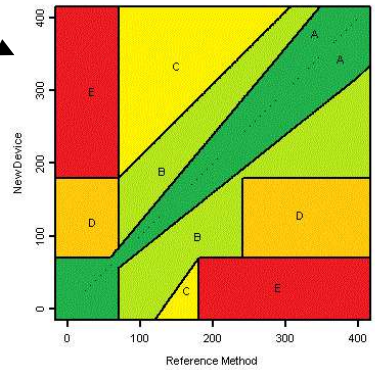
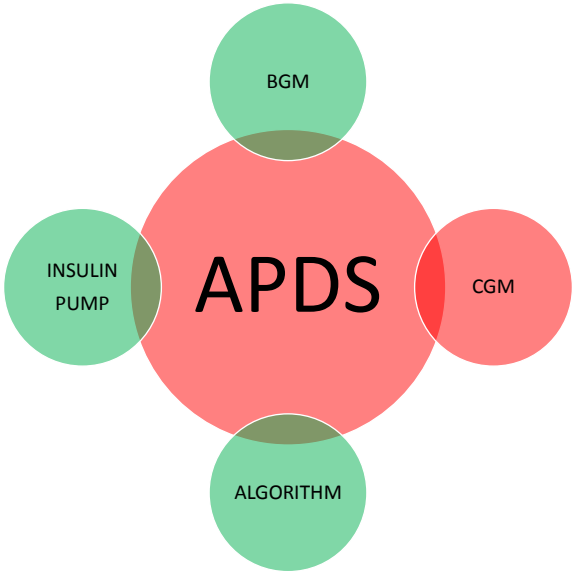
BGM PERFORMANCE ASSESSMENT

- 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

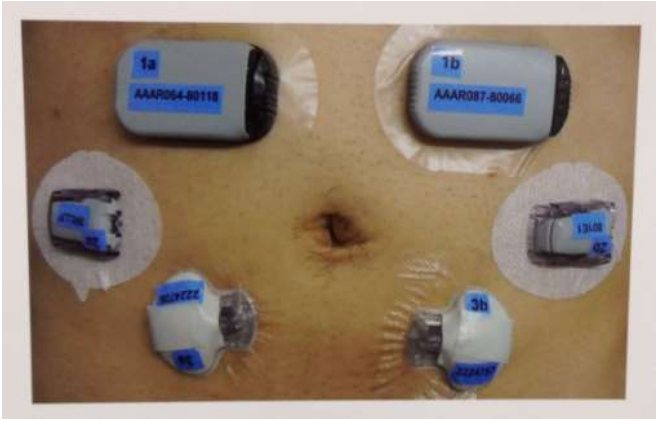
- IMPLANTABLE SYSTEMS
  Senseonics "Eversense"
  Eyesense
  Glysens

- FLASH GLUCOSE MONITOR (on demand)
  Abbott Freestyle Libre (factory calibrated)

HOW ACCURATE DO CGM's NEED TO BE ?

MARD = ?

THE REAL CGM COMPARISON…..



	MARD
NAVIGATOR (ABBOTT)	12.4 ± 3.6
GUARDIAN (MEDTRONIC)	16.4 ± 6.9
SEVEN PLUS (DEXCOM)	16.7 ± 3.8

Freckmann G, Pleus S et al
J Diabetes Sci Technol. 2013 Jul 1;7(4):842-53

SENSOR ACCURACY

Accuracy and sensing performance

When **LOWER** is better
Overall Accuracy: Mean ARD (MARD)* % of CGM-YSI

	Mean ARD (MARD)*
New study Dexcom G4 PLATINUM w/ NEW Software 505	9%
PREVIOUS STUDY Dexcom G4 PLATINUM	13%

*CGM accuracy is measured by the mean absolute relative difference (MARD) from a paired reference value obtained from clinical glucose measurements from a lab analyzer. YSI (Yellow Springs Instrument) A lower value indicates closer accuracy to reference values.

When **HIGHER** is better
Hypoglycemia (CGM ≤ 80mg/dL) Accuracy over Time: Percentage of CGM within 20 mg/dL of YSI

	Day 1	Day 4	Day 7	Avg Daily Calibration
New study Dexcom G4 PLATINUM w/ NEW Software 505	93%	95%	97%	2x/day
PREVIOUS STUDY Dexcom G4 PLATINUM	83%	88%	85%	2x/day

The sensors performance was evaluated in two separate prospective clinical studies. Differences between the studies include the number of subjects enrolled, the number of sensors worn by each participant, the MARD, mean values, and the number of clinic days each subject participated in during the study.

DEXCOM website….

SENSOR ACCURACY

Table 56. MARD by FST Day and Glucose Reference Range, Using Sensor Performance Data from the 640G System (640G Pump, Enlite 3 Sensor and GST3C Transmitter), Abdominal Insertion

Reference Range	Characteristic	FST 1	FST 3	FST 7	Total
A) <=75 mg/dL	N of Paired Points	481	627	412	1520
	Mean (SD)	16.95 (13.53)	12.62 (10.42)	12.84 (10.80)	14.05 (11.75)
	Median	14.81	10.96	9.45	11.28
	Min, Max	0.00, 79.86	0.00, 68.41	0.00, 48.99	0.00, 79.86
B) >75-180 mg/dL	N of Paired Points	2360	2577	1858	6795
	Mean (SD)	12.63 (11.16)	8.74 (7.99)	8.76 (8.45)	10.10 (9.51)
	Median	9.26	6.54	6.12	7.25
	Min, Max	0.00, 66.94	0.00, 68.10	0.00, 55.91	0.00, 68.10
C) >180 mg/dL	N of Paired Points	1453	1329	993	3775
	Mean (SD)	12.39 (9.67)	7.55 (5.77)	9.61 (8.78)	9.95 (8.50)
	Median	10.54	6.56	7.05	7.96
	Min, Max	0.00, 63.14	0.00, 33.87	0.00, 55.04	0.00, 63.14
Overall	N of Paired Points	4294	4533	3263	12090
	Mean (SD)	13.04 (11.07)	8.93 (7.97)	9.53 (8.97)	10.55 (9.62)
	Median	10.22	6.93	6.8	7.84
	Min, Max	0.00, 79.86	0.00, 68.41	0.00, 55.91	0.00, 79.86

SENSOR ACCURACY

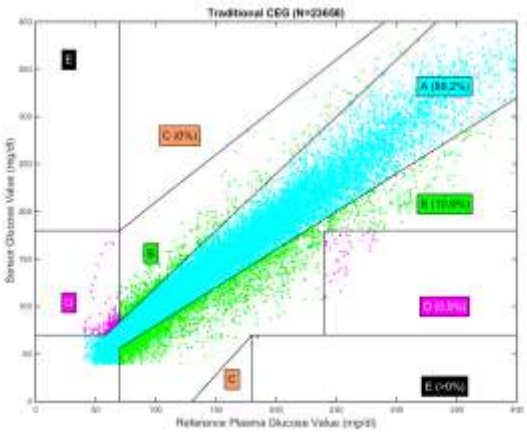


Table 10. Values in Continuous Error Grid Zones; Combined Analyses for the 640G System (640G Pump, Enlite 3 Sensor and GST3C Transmitter) and the Guardian Mobile System (Guardian Mobile Application, Enlite 3 Sensor, GST4C Transmitter), Using Actual Calibration, Number (%), Abdominal Insertion

Clarke Error Grid Zone	Comparative Glucose Reference Range				
	All Ranges	40-80 mg/dL	>80-120 mg/dL	>120-240 mg/dL	>240-400 mg/dL
A+B	2349 (99.2%)	3460 (96.2%)	5651 (100.0%)	11309 (100.0%)	3060 (96.7%)
A	21315 (90.1%)	3195 (88.8%)	4907 (86.8%)	10373 (91.7%)	2840 (91.8%)
B	2165 (9.2%)	265 (7.4%)	744 (13.2%)	936 (8.3%)	220 (7.1%)
C	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
D	177 (0.7%)	138 (3.8%)	0 (0.0%)	0 (0.0%)	39 (1.3%)
E	1 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)
Overall	23658 (100.0%)	3598 (15.2%)	5651 (23.9%)	11310 (47.8%)	3099 (13.1%)

SENSOR ACCURACY

MANUFACTURER	DEVICE	MARD % %
MEDTRONIC	GUARDIAN	16
MEDTRONIC	ENLITE 3 (4th Generation)	9.6 *
DEXCOM	SEVEN PLUS	16
DEXCOM	G5	9.0 *
ABBOTT	FREESTYLE LIBRE FLASH	10.7 *
ABBOTT	FREESTYLE NAVIGATOR	12.3

Senseonics Continuous Glucose Monitoring System

Sensor
(subcutaneous)

Body-Worn Transmitter

Smartphone with Senseonics Mobile Medical App

Insertion Tools
(Blunt Dissector and Sensor Inserter)

PC-Based Transmitter Manager

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"EVERSENSE CGM"

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

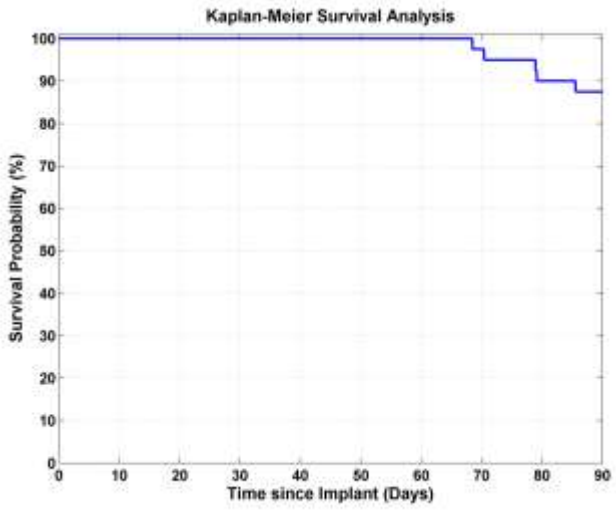
SENSEONICS …..Sensor Accuracy

Site	Sensor to Lab (Clinic Sessions)		Sensor to FS (Home Use)	
	Glucose >75mg/dL MARD (%)	Glucose <75mg/dL MAD (mg/dL)	Glucose >75mg/dL MARD (%)	Glucose <75mg/dL MAD (mg/dL)
Site 1	10.4 (0.6)	6.8 (0.4)	13.3 (0.8)	12.9 (0.6)
Site 2	12.8 (0.7)	12.2 (0.7)	15.3 (0.8)	23.7 (2.4)
Site 3	11.9 (0.7)	15.0 (1.0)	15.0 (0.9)	15.0 (0.9)
Site 4	10.7 (0.6)	13.4 (0.7)	13.3 (1.0)	13.5 (1.0)
Site 5	9.9 (0.5)	13.9 (0.7)	13.2 (0.8)	14.0 (0.9)
Site 6	12.8 (0.7)	15.6 (0.9)	14.2 (0.8)	14.6 (1.0)
Combined Accuracy	**11.4 (0.7)**	**13.5 (0.8)**	**14.0 (0.8)**	**15.3 (1.1)**

CE Mark Submission, Primary Effectiveness End Point

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

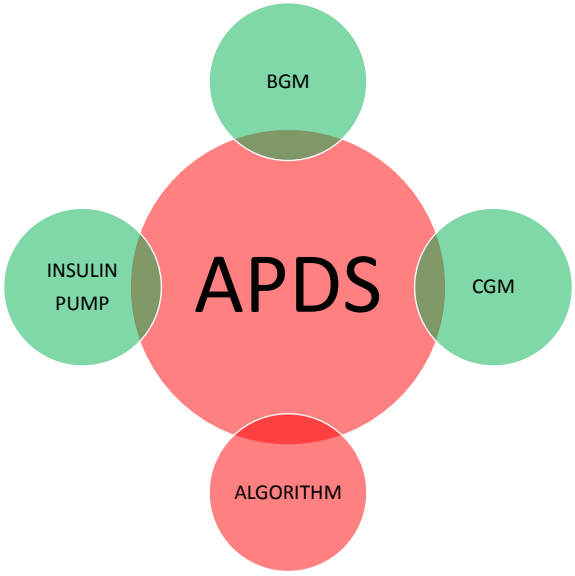
SENSEONICS….Survivability Analysis



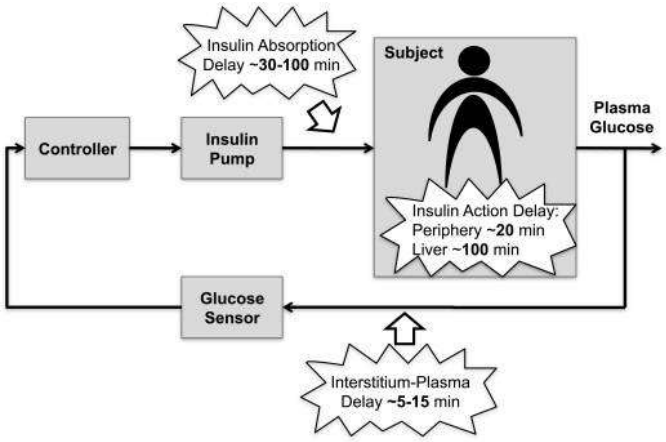
HOW ACCURATE DO CGM's NEED TO BE ?

MARD < 10 %

CLOSING THE LOOP – ALGORITHM



DELAYS IN CLOSED LOOP CONTROL

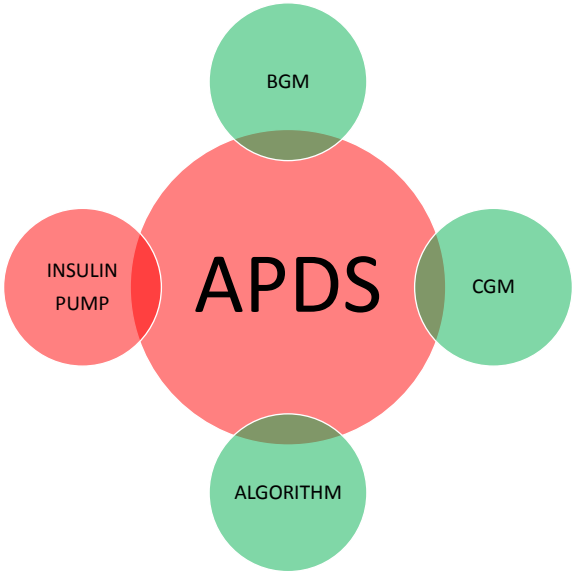


Cobelli et al, DIABETES 2011

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

CLOSING THE LOOP-
AUTOMATION OF INSULIN ADMINISTRATION

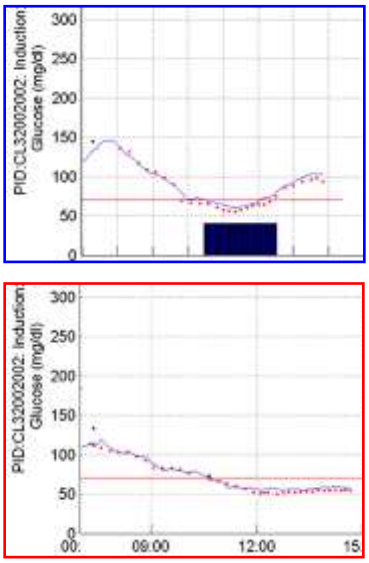


The Iterative Steps to the Automation of Insulin Administration

- 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



LGS ON
Hypo Duration = 154 minutes
Nadir = 55.5 mg/dL
AUC<70 = 1163 mg/dL*min

	DURATION OF HYPO	NADIR mg/dl	END OBS mg/dl
LGS ON	138.5 min	59.6	91.4
LGS OFF	170.7 min	57.6	66.2
p-VALUE	0.006	0.015	<0.001

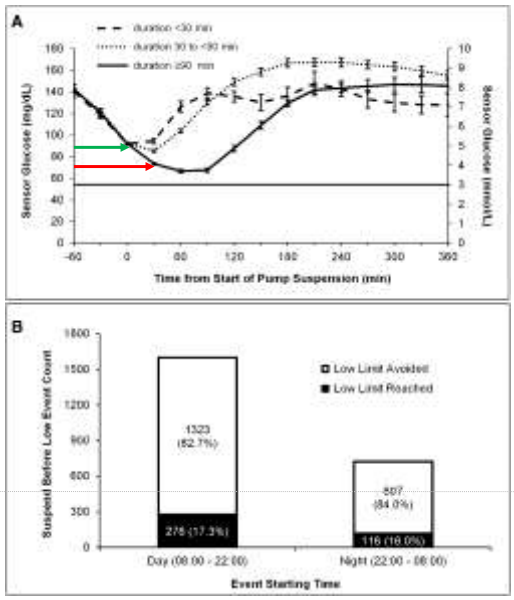
LGS OFF
Hypo Duration = 248 minutes
Nadir = 50.3 mg/dL
AUC<70 = 3493 mg/dL*min

Satish Garg, Ronald L. Brazg, Timothy S. Bailey, Bruce A. Buckingham, Robert H. Slover, David C. Klonoff, John Shin, John B. Welsh, and Francine R. Kaufman. Diabetes Technology & Therapeutics. March 2012, 14(3): 205-209

PLGM

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

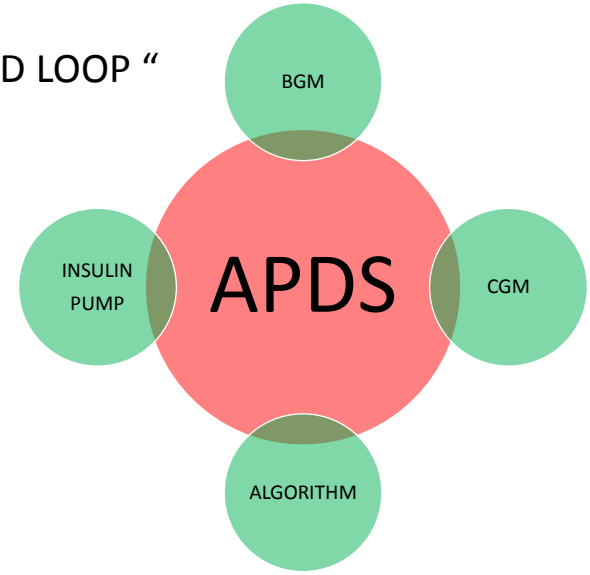
The SmartGuard system suspends insulin delivery if the SG level is predicted to drop below 20 mg/dL (1.1 mmol/L) above the preset low limit within the next 30 min.



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 "



OPEN LOOP……

AVE SG
191 mg/dl

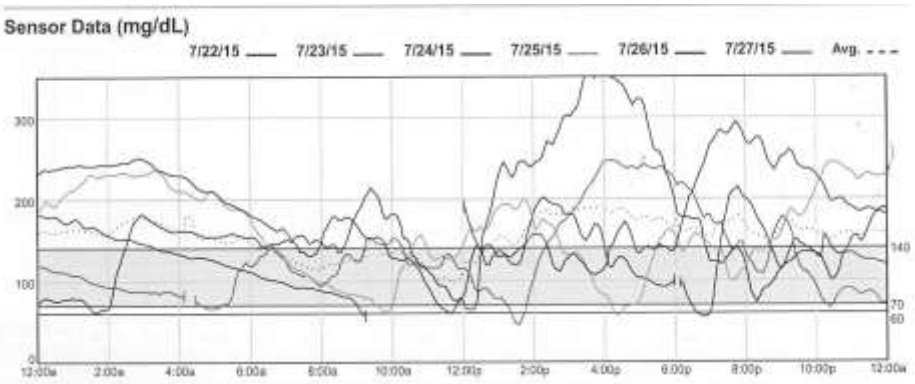
CLOSING THE LOOP. ……IN HCL 1 WEEK

AVE SG
146 mg/dl

CLOSING THE LOOP…..IN HCL 4 WEEKS

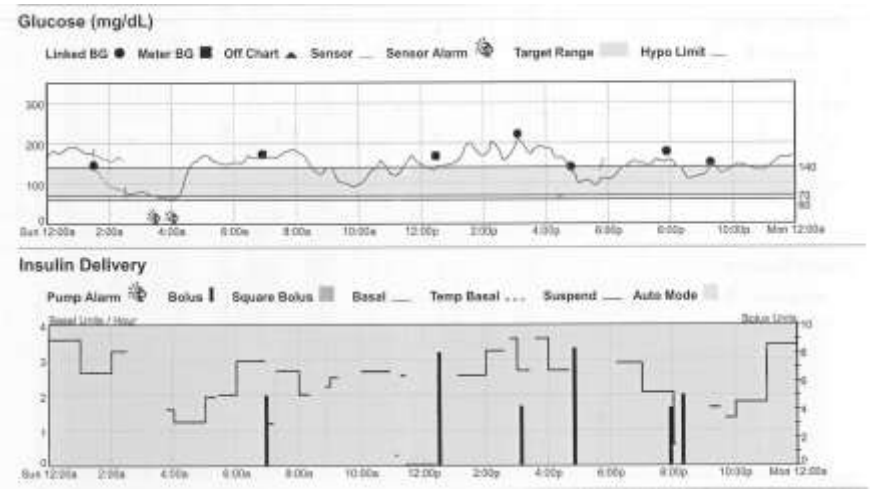
AVE SG
131 mg/dl

PRE HCL…..AVE SG (126-182mg/dl)

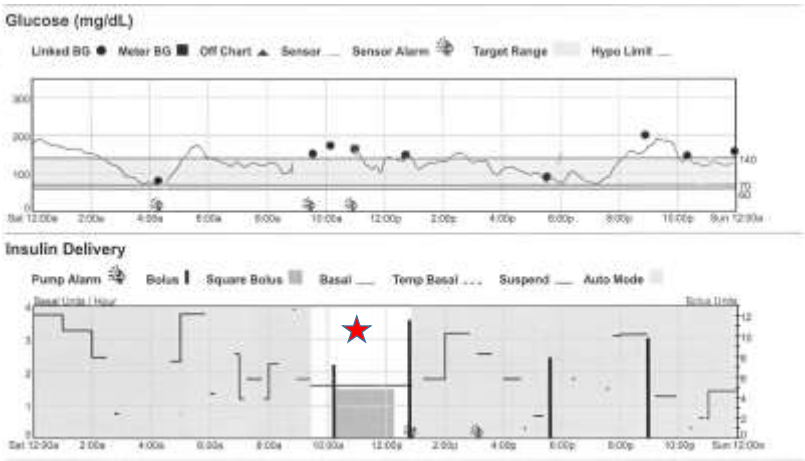


	Wed Jul 22	Thu Jul 23	Fri Jul 24	Sat Jul 25	Sun Jul 26	Mon Jul 27	Average / Total
# Sensor Values	143	286	288	288	288	111	1,403
High SG (mg/dL)	214	247	356	245	294	181	356
Low SG (mg/dL)	55	46	61	57	59	57	46
Average SG (mg/dL)	139	129	168	160	182	126	155
Standard Dev.	37	51	74	52	56	33	59
MAD %	N/A	N/A	N/A	N/A	N/A	N/A	N/A
# Valid Calibrations	3	6	4	4	4	1	22

IN HCL……(AVE SG 143 mg/dl)



IN HCL……(AVE SG 127mg/dl)

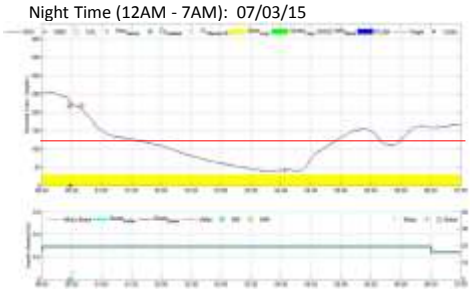


HYBRID CLOSED LOOP

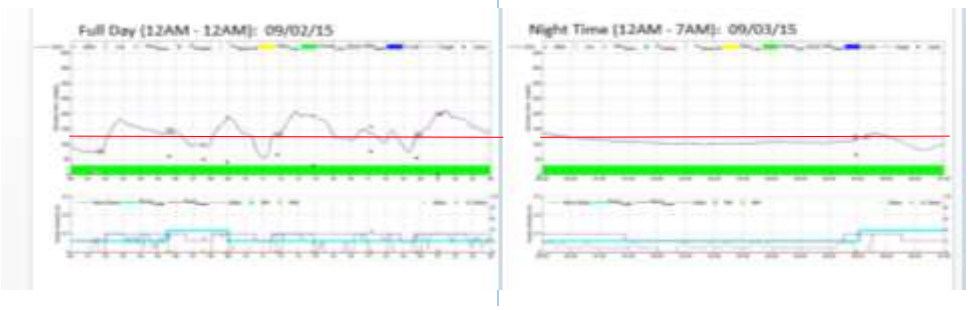
OPEN LOOP

Full Day (12AM - 12AM): 07/02/15

Night Time (12AM - 7AM): 07/03/15



CLOSED LOOP



FAILURE IS NOT AN OPTION…….

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

AUTOMATION OF INSULIN DELIVERY

2016
"HYBRID CLOSED LOOP"

……PLGM……..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