UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AGAMATRIX, INC.

Petitioner

v.

DEXCOM, INC.

Patent Owner

U.S. PATENT NO. 9,724,045

TITLE: SYSTEMS AND METHODS FOR REPLACING SIGNAL ARTIFACTS IN A GLUCOSE SENSOR DATA STREAM

Case No. IPR2018-01715

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,724,045

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Citations in this petition to patents use the column and line number found within the document, rather than the page indicated by the exhibit label. Citations to the remaining exhibits refer to the page number of the underlying document.

PETITION FOR *INTER PARTES* REVIEW

Pursuant to 35 U.S.C. § 311 and 37 C.F.R. § 42.100 *et seq.*, Petitioner AgaMatrix, Inc. ("AgaMatrix," or "Petitioner") petitions the Patent Trial and Appeal Board to institute an *Inter Partes* Review ("IPR") of claims 16-21, 23-25, 37-39, and 41-43 ("challenged claims") of U.S. Patent No. 9,724,045 ("the '045 Patent," Ex. 1001) currently assigned to Dexcom, Inc. ("Dexcom" or "Patent Owner").

I. INTRODUCTION

The '045 Patent relates generally to signal processing in a glucose sensor. In particular, the challenged claims are directed to glucose sensor systems which employ sensor electronics to apply voltage(s) to an electrochemical glucose sensor, to measure a signal response of the sensor, and to evaluate the severity of a signal artifact in order to decide whether to accept or discard a measurement.

This was not a new idea before the priority date of the '045 Patent. Multiple prior art references disclose similar glucose sensors and related error-detection and error-rejection techniques. Ex. 1003, ¶¶ 86-117.

For example, U.S. Patent No. 6,233,471 ("Berner," Ex. 1005), discloses a signal processing method for continually or continuously measuring blood glucose concentration using a glucose sensor system such as a GlucoWatch™. Berner's biosensor includes an electrochemical cell and sensor electronics which apply and

switch voltages to the cell to measure raw glucose signals. Berner also teaches applying various data screens to invalidate or correct poor or incorrect signals based on predetermined criteria. Berner further teaches correcting the raw glucose signal by removing "baseline background" signal and reporting glucose concentrations.

U.S. Patent No. 5,497,772 ("Schulman," Ex. 1008), in the same field of continuous glucose monitoring as Berner, discloses all the user interface limitations recited in the challenged claims.

Since at least these prior art references disclose, teach or suggest all the elements of the challenged claims, as shown in this Petition, the cited references render all the challenged claims obvious. Ex. 1003, ¶¶ 12-13.

II. TECHNOLOGY BACKGROUND

The technology at issue in the challenged claims relates to electrochemical glucose monitors and signal processing. Ex. 1003, ¶¶ 38-39.

A. Electrochemical Glucose Measurement

Glucose sensors typically come in two forms: Blood Glucose Meter (BGM) or Continuous Glucose Monitor (CGM), both well known long before the priority date of the challenged claims. In general, BGMs provide episodic measurements of glucose outside the body while CGMs provide continuous monitoring of glucose inside the body. Ex. 1003, ¶ 40.

For each glucose measurement with a BGM device, a patient must prick his/her finger to extract a new blood sample and apply that sample to a single-use test strip inserted into the BGM device. An electrochemical reaction between the blood glucose and the chemicals on the test strip allows the blood sample to be analyzed to determine the glucose level in the blood at the time the blood is extracted. Ex. 1003, ¶ 41.

CGMs, on the other hand, monitor glucose levels on a continuous basis and therefore typically involve implanting a device into the patient's body or attaching a device thereto. Since the implanted or attached CGM device is constantly exposed to a complex environment in or on the patient's body, the device tend to pick up interferences (*i.e.*, noises) from the body and from other conditions in the body not picked up by BGMs. Therefore, compared to BGMs, CGMs typically require more signal processing to correct for the extensive interferences that they detect. Ex. 1003, ¶ 42.

Glucose levels are typically determined based on electrochemistry. When a voltage is applied between two electrodes in a solution containing the glucose (*e.g.*, a blood sample), electrochemical reactions at the electrodes may result in the consumption or release of electrons thereby generating an electric current in an external circuit indicative of the glucose concentration in the chemical reaction. Ex. 1003, ¶ 43; *see also id*., ¶¶ 44-55.

It has long been discovered that, when a potential is applied to two electrodes dipped in an analyte solution, such electric current is diffusion-limited and its decay over time can be described with the following Cottrell equation (derived by Frederick Gardner Cottrell in 1903):

$$i = \frac{nFAc_j^0\sqrt{D_j}}{\sqrt{\pi t}}$$

where *i* denotes the measured current, *n* denotes the number of electrons (to reduce/oxidize one molecule of analyte *j*, such as a glucose molecule), *F* denotes Faraday constant, *A* denotes the area of the (planar) electrode, c_j^0 denotes the initial concentration of the oxidizable analyte *j*, D_j denotes the diffusion coefficient for species *j*, and *t* denotes time. Ex. 1011, pp. 162-163; Ex. 1003, ¶ 56.

According to the Cottrell equation, the current value (*i*) is inversely proportionate to the square root of time (*t*), and the slope of current plotted against $1/\sqrt{t}$ bears a linear relationship to the initial analyte concentration (c_j^0). As a result, the greater the concentration of analyte (c_j^0) in the chemical reaction, the greater the resulting electric current (*i*), thereby allowing glucose concentration to be determined by measuring a current—a method known as amperometry or chronoamperometry. Ex. 1003, ¶ 57

The amperometric method for glucose sensing and sensor devices implementing such a method were well known in the art since at least the 1980s.

See, *e.g.*, Nankai (Ex. 1009); Pottgen (Ex. 1010) (both disclosing amperometric techniques for determining glucose concentration). Ex. 1003, ¶ 58.

B. Error-Detection & Error-Rejection

Similarly, signal processing techniques, especially the concept of error-detection and error-rejection (*i.e.*, keeping good data and rejecting bad data), were generally known to those having ordinary skill in the art. Ex. 1003, ¶ 60. In particular, it was desirable and well known, based at least on common sense, to detect signal errors and/or noises so as to reject measurements when the errors or noises are too severe. Indeed, various methods for screening and rejecting noisy or erroneous signals were well known, well understood, and applied in the glucose sensing art. Ex. 1003, ¶ 59.

For example, U.S. Patent No. 6,558,351 ("Steil," Ex. 1012), which is also in the field of glucose sensors, teaches evaluating measurement data against noise thresholds and discarding the data "if more than three values are outside of the noise thresholds." Steil, 23:24-33. Likewise, U.S. Patent No. 4,832,034 ("Pizziconi," Ex. 1013) teaches using a microprocessor in a glucose sensor to "discard artifacts" and "to automatically measure and compensate for temperature changes." Pizziconi, 23:58-65. *See also* U.S. Patent No. 6,309,884 ("Cooper," Ex. 1014), 9:3-50 (disclosing a number of error analysis methods which reject the entire glucose measurement session when the data meet certain criteria); U.S.

Patent No. 6,153,069 ("Pottgen-069," Ex. 1015), 4:42-65 (disclosing the use of a calibration curve to identify abnormal amperometric glucose measurements that deviate from the expected Cottrell relationship). Ex. 1003, ¶ 61.

III. OVERVIEW OF THE '045 PATENT

A. Prosecution History

The '045 Patent issued from U.S. Patent Application No. 15/481,347, filed April 6, 2017, which is a continuation of U.S. Patent No. 9,649,069 ("the '069 Patent"). The '069 Patent, in turn, is a continuation patent in a line of continuations, tracing back to U.S. Patent Application No. 10/648,849, filed Aug. 22, 2003 (now U.S. Patent No. 8,010,174).

On April 20, 2017, the applicant submitted two Information Disclosure Statements citing over 1,200 references, without providing any explanation or guidance to the examiner. Ex. 1002, 230-298, 301-309.

In the next few weeks, the applicant communicated with the examiner primarily through a series of telephonic interviews and a few preliminary amendments. *See* Ex. 1002, 228, 167, 53 (interview summaries); 177-187, 193-203, 208-222 (preliminary amendments).

On June 1, 2017, a Notice of Allowance was issued without stating any reason for allowing the claims or discussing any of the 1,200 cited references. *Id*., 43-45. On June 21, 2017, a Corrected Notice of Allowance was issued, again

without stating any reason for allowing the claims or discussing any of the 1,200 cited references. *Id*., 36-39.

The ’045 Patent issued on August 8, 2017. *Id*., 2; Ex. 1001, 1.

B. Summary of the Disclosure

The ’045 Patent is directed to systems and methods for processing data received from glucose sensors, specifically continuous glucose monitors. FIG. 1 illustrates such a glucose sensor 10:

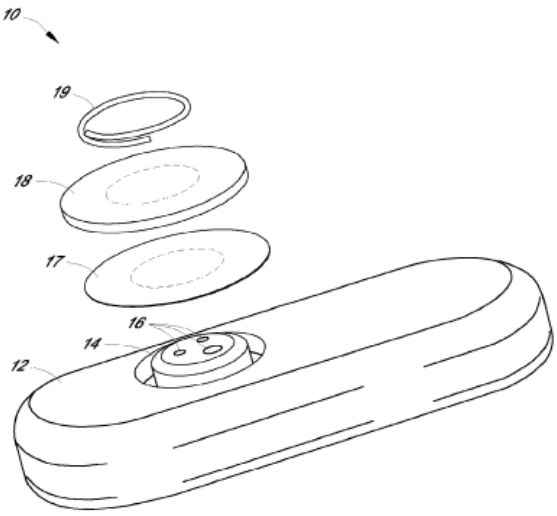

FIG. 1

Ex. 1001, FIG. 1; Ex. 1003, ¶¶ 62-63.

The glucose sensor 10 includes three electrodes 16. Ex. 1001, 20:25-27. An enzyme contained in the sensing membrane 17 “catalyzes the conversion of oxygen and glucose to hydrogen peroxide and gluconate.” *Id.*, 20:45-49; Ex. 1003, ¶ 64.

Electronics connected to the electrodes measure the amount of hydrogen

peroxide (H_2O_2) and this correlates to the amount of glucose in the sample, which is consistent with the prior art electrochemical glucose sensing method described above. Ex. 1001, 20:41-59; Ex. 1003, ¶¶ 65-66.

The preferred embodiment disclosed in the '045 Patent is a continuous glucose monitor (CGM)—*i.e.*, a "system [that] monitors a data stream[1] from a glucose sensor." Ex. 1001, Abstract. *See also id.*, 15:65-16:3; Ex. 1003, ¶¶ 67-69.

Being implanted in the body, the CGM of the '045 Patent captures interferences from other conditions and sources in the body, causing significant signal errors. The disclosed CGM device purports to detect signal errors and make appropriate corrections. Figure 7A is a graph of a raw data stream, from a glucose sensor and spanning about four hours, that includes a signal artifact (in region 74a):

[1] "The terms 'raw data stream' and 'data stream,' as used herein … broadly encompass a plurality of time spaced data points from a substantially ***continuous*** glucose sensor, which comprises individual measurements taken at time intervals ranging from fractions of a second up to, e.g. 1, 2, or 5 minutes or longer." Ex 1001, 14:15-26 (emphasis added).

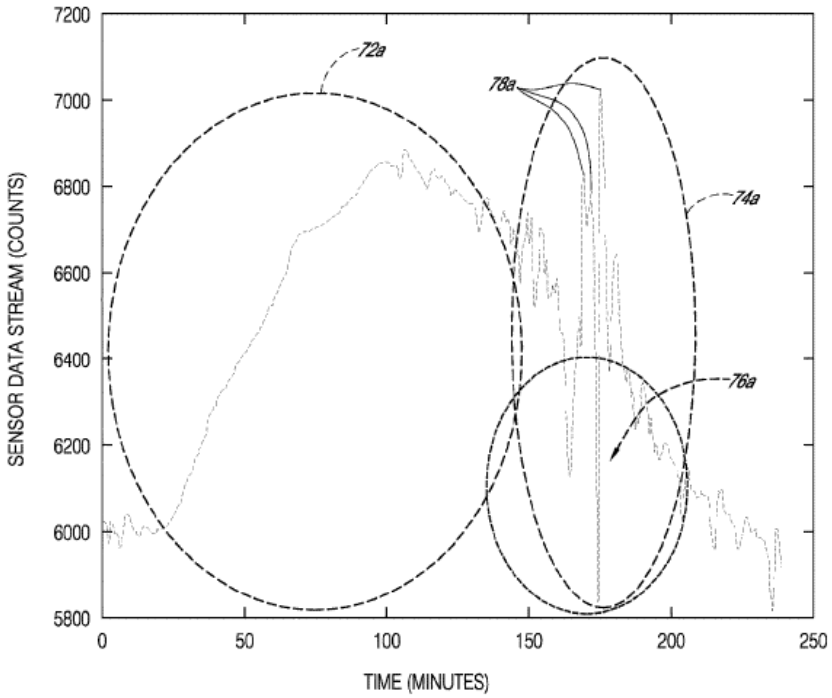

FIG. 7A

Ex. 1001, FIG. 7A; Ex. 1003, ¶¶ 67, 70-71.

Despite providing no meaningful discussion of any embodiment other than CGM in the specification, the patent nevertheless claims:

> "***The glucose sensor can be <u>any</u> device capable of measuring the concentration of glucose.*** One exemplary embodiment is described below, which utilizes an implantable glucose sensor. However, it should be understood that ***the devices and methods described herein can be applied to <u>any</u> device capable of detecting a concentration of glucose and providing an output signal that represents the concentration of glucose***."

Ex. 1001, 20:11-18 (emphasis added). To the extent this characterization is true, the inventive contribution of the challenged claims, if any, is not in sensor

hardware or any specific glucose measurement methodology. Indeed, the challenged claims only recite generic, well-known sensor components and measurement operations. Nor is the claimed signal processing method novel or inventive since it merely applies a basic concept of error-detection and/or error-rejection to glucose data. Ex. 1003, ¶¶ 72-73.

C. Challenged Claims

The claims at issue in this Petition are claims 16-21, 23-25, 37-39, and 41-43, among which claims 16 and 37 are independent claims.

Claim 16 reads:

[16.preamble] A glucose sensor system, the system comprising:

[16.a] an electrochemical glucose sensor configured to be in contact with a biological sample for measuring a glucose concentration, wherein the electrochemical glucose sensor comprises a first electrode, a second electrode, and an enzyme-containing film;

[16.b] sensor electronics comprising a processor for executing a computer program code stored in a memory to cause the sensor electronics to:

[16.c] apply a voltage to the electrochemical glucose sensor at a first setting,

[16.d] switch the voltage applied to the electrochemical sensor to a different setting,

[16.e] measure a signal response of the electrochemical glucose sensor responsive to the switching,

[16.f] evaluate a severity associated with a signal artifact based on the

measured signal response of the electrochemical glucose sensor to the switching, wherein the signal artifact is associated with a non-glucose rate limiting phenomenon, and

[16.g] generate an estimated glucose concentration value when the severity associated with the signal artifact is evaluated to be under a predetermined threshold, wherein the estimated glucose concentration value accounts for the severity associated with the signal artifact; and

[16.h] a user interface configured to display the estimated glucose concentration value.

Independent claim 37 includes almost identical limitations as independent claim 16 except that claim 37 recites "wherein the measured signal response is a time-varying voltage response of the electrochemical glucose sensor" and adds more "user interface" functions.

Thus, the overlapping limitations of the independent claims may be sorted into hardware elements and software elements. The hardware elements include: "an electrochemical glucose sensor …," "sensor electronics comprising a processor …," and "a user interface …." The software elements include the steps of "apply" and "switch" a voltage, "measure a signal response …," "evaluate a severity …," and "generate an estimated glucose concentration value …" Ex. 1003, ¶¶ 78-79.

As noted above, the universal applicability of the patent disclosure (as claimed in the specification) suggests that the combination of hardware elements is

not novel or inventive. Indeed, those recited hardware elements are generic to any electrochemical glucose sensor device and were well known in the art. Ex. 1003, ¶¶ 80-81.

Furthermore, the recited software elements (or functional steps) involve nothing more than basic operations of an electrochemical glucose sensor and the well-known signal processing concept of error-detection and error-rejection—that is, generating and displaying a glucose value only if a detected signal error is not too severe. Ex. 1003, ¶ 82.

Thus, the claimed invention is really directed to a broad, abstract concept of keeping good data and rejecting bad data—an idea that is basic and fundamental to any signal processing task—applied here to the basic operations of a generic electrochemical glucose sensor. It is then not surprising that, as shown in detail below, all of the claimed hardware elements, their operations, and the recited signal processing concepts, are indeed conventional, routine and well-known to the art. Ex. 1003, ¶ 83.

IV. STATEMENT OF THE RELIEF REQUESTED

A. Claims for Which Review is Requested and the Statutory Grounds of Challenge

Petitioner respectfully requests that the Board institute an IPR of claims 16-21, 23-25, 37-39, and 41-43 of the ’045 Patent and cancel those claims as unpatentable under pre-AIA 35 U.S.C. § 103, based on the following grounds:

Ground	*Statute*	*References*	*Claims*
1	§ 103	Berner	16-21, 23-25
2	§ 103	Berner, Schulman	37-39, 41-43

The grounds for unpatentability rely on the following references, which qualify as prior art under pre-AIA 35 U.S.C. § 102:

Exhibit.	*Prior art*	*Filing/Issued/Publication Date*	*Statute*
1005	U.S. Patent No. 6,233,471 ("Berner")	Filed May 11, 1999 Issued May 15, 2001	102(a)/(b)
1008	U.S. Patent No. 5,497,772 ("Schulman")	Filed Nov. 19, 1993 Issued March 12, 1996	102(a)/(b)

Petitioner's arguments here were not considered by the Examiner, and Petitioner presents additional evidence not considered by the PTO, including the declaration of John L. Smith, Ph.D. (Ex. 1003). Dr. Smith has over 55 years of experience in electrochemical analytical instruments and systems, including 30 years in the glucose monitoring field. From his extensive experience in the field, Dr. Smith has unparalleled knowledge of the glucose monitoring technology and its development history. Ex. 1003, ¶¶ 5-11.

The Berner (Ex. 1005) and Schulman (Ex. 1008) patents were among the more than 1,200 references disclosed to the Patent Office (including seven Berner patents and applications) in an Information Disclosure Statement, which contained no explanation regarding the references and provided the examiner with no

guidance regarding which of the more than 1,200 cited reference were most pertinent to the claimed inventions. Ex. 1002, 230-298, 305-309. The prosecution history confirms that neither patent (nor their combination) was discussed by the examiner and there is no evidence in the prosecution history how closely these two references out of the 1,200 cited references were analyzed by the examiner, if at all. *See* Ex. 1002; Ex. 1003, ¶ 114.

B. Level of Ordinary Skill

As explained by Dr. Smith, who is an expert in this field, a person of ordinary skill in the art ("POSITA") at the time of the alleged invention would have had the equivalent of either (i) a bachelor's or master's degree in biology, chemistry, physics, electrical engineering, or related fields, and at least five years of experience developing glucose sensors or other biosensensors; or (ii) a Ph.D. with at least two years of experience in the same fields. Additional graduate education could substitute for professional experience, and significant work experience could substitute for formal education. Ex. 1003, ¶¶ 33-36.

V. CLAIM CONSTRUCTION

In an *inter partes* review, the claim terms should be given their plain meanings according to the broadest reasonable interpretation in light of the

specification.[2] *See Cuozzo Speed Technologies, LLC v. Lee*, 136 S.Ct. 2131 (2016).

In the related ITC proceeding (Investigation No. 337-TA-1075), the parties agreed on the interpretation of some claim terms, the judge construed some of the disputed terms, and Patent Owner offered "plain and ordinary meaning" interpretation of other disputed terms. Those terms, to the extent relevant to the challenged claims, are listed below. Petitioner believes that the broadest reasonable interpretation of the below-listed claim terms is *at least as broad as* the listed definitions.

Claim Term	Definition	Source[3]
electrochemical glucose sensor	a device by which glucose can be quantified in which chemical energy is converted to electrical energy	Parties
enzyme-containing film	a thin layer that includes an enzyme	Pat. Owner

[2] Petitioner reserves the right to present different constructions in other forums (*e.g.*, a district court, or the ITC) where a different claim construction standard applies.

[3] *See* Ex. 1016, 14-15 ("Construction of the Agreed-Upon Claim Terms"); *id*. at 24, 28, 30, 37, 40 (judge-ordered definitions); *id*., 36 (Dexcom's proposed definition of "signal artifact"); Ex. 1017, 20 (fn. 7), 42-43, 50 (Dexcom's proposed definition of "enzyme-containing film").

apply a voltage to the electrochemical glucose sensor at a first setting	put to use a voltage to the electrochemical glucose sensor at a first specified condition	ITC judge
switch the voltage applied to the electrochemical sensor to a different setting	change the voltage that was put to use at the electrochemical glucose sensor to a different specified condition	ITC judge
signal artifact	a particular type of noise an artifact relating to signal noise	ITC judge Pat. Owner
non-glucose rate limiting phenomenon	a condition, other than glucose, that affects an electrochemical reaction rate of the electrochemical glucose sensor	Parties
generate an estimated glucose concentration value when the severity associated with the signal artifact is evaluated to be under a predetermined threshold	to generate an estimated glucose concentration value for display to a user when the severity related to the signal artifact (as defined herein) is evaluated by the sensor electronics to be less than a predetermined threshold value	Parties
wherein the estimated glucose concentration value accounts for the severity associated with the signal artifact	wherein the degree of the signal artifact is taken into account in the estimated glucose concentration value	ITC judge
a voltage response of the electrochemical glucose sensor	voltage responsive to a condition of the electrochemical glucose sensor	ITC judge
available electrode surface area	surface area of an electrode where an electrochemical reaction occurs	Parties

VI. DETAILED GROUNDS FOR UNPATENTABILITY

A. Ground 1: Claims 16-21 and 23-25 are obvious under 35 U.S.C. § 103 in light of Berner.

Berner (Ex. 1005) renders each of claims 16-21 and 23-25 obvious. Ex. 1003, ¶ 119.

1. Independent Claim 16

i. Berner discloses the preamble.

To the extent that the preamble is limiting, Berner discloses "[a] glucose sensor system." Ex. 1003, ¶ 120.

Berner discloses "methods for continually or continuously measuring the concentration of target chemical analytes present in a biological system" and notes in particular that "[o]ne important application of the invention involves ***a method for monitoring blood glucose concentrations***." Berner, 1:14-20 (emphasis added). *See also id*., Abstract. In Berner's preferred embodiments, "the analyte is a physiological analyte of interest, for example ***glucose*** …" *Id*., 3:15-18 (emphasis added). *See also id*., 5:46-59 (identifying glucose as an example of "analyte" in preferred embodiments); 10:39-57 (same); 7:53-65 (identifying glucose monitor as an example of "sensing device" in its definition); 34:55-36:38 (describing "Signal Processing for Measurement of Blood Glucose" in the only example of the invention) (emphasis added). Ex. 1003, ¶¶ 121-122.

Therefore, Berner discloses the preamble of claim 16. Ex. 1003, ¶ 123.

ii. Berner discloses, teaches or suggests "an electrochemical glucose sensor configured to be in contact with a biological sample for measuring a glucose concentration, wherein the electrochemical glucose sensor

comprises a first electrode, a second electrode, and an enzyme-containing film" (Element [16.a]).

(1) "an electrochemical glucose sensor configured to be in contact with a biological sample for measuring a glucose concentration"

Berner discloses "an electrochemical glucose sensor … for measuring a glucose concentration" because Berner describes a biosensor comprising "an electrochemical sensing element" used for measuring "blood glucose values." Berner, 2:59-61 ("In preferred embodiments of the invention, a biosensor is used which comprises an ***electrochemical sensing element***."); 3:15-18 ("In preferred embodiments, the analyte is a physiological analyte of interest, for example ***glucose*** …") (emphasis added). "In particularly preferred embodiments, a sampling device is used …, and ***the analyte of interest is glucose***." Berner, 13:34-41 (emphasis added). Ex. 1003, ¶ 124.

Berner's biosensor is also "configured to be in contact with a biological sample":

> "The raw signal can be obtained using any suitable sensing methodology including, for example, methods which rely on ***direct contact of a sensing apparatus with the biological system***; methods which extract samples from the biological system by invasive, minimally invasive, and non-invasive sampling techniques, wherein ***the sensing apparatus is contacted with the extracted sample***; methods which rely on ***indirect contact of a sensing apparatus with the biological***

system; and the like …

In one particular embodiment of the invention, the raw signal is obtained using ***a transdermal sampling system that is placed in operative contact with a skin or mucosal surface of the biological system*** . . . ***The transdermal sampling system is maintained in operative contact with the skin or mucosal surface of the biological system to provide for such continual or continuous analyte measurement.***"

Berner, 2:43-3:4 (emphasis added). Ex. 1003, ¶ 125.

It is well known in the art that at least the enzyme portion of an electrochemical glucose sensor has to come in contact with the biological sample in order to react with any glucose content therein. *See*, *e.g.*, Berner, 14:18-24 ("… glucose is extracted into the hydrogel collection pad where it contacts the GOx enzyme."). Therefore, the collection pad in Berner's sensor must be in contact with a biological sample. Ex. 1003, ¶ 126.

Moreover, since either "the skin or mucosal surface of the biological system" or the "extracted sample" (*e.g.*, biological fluid containing glucose) constitutes a "biological sample," at least a part of Berner's biosensor (including its transdermal sampling system) is "configured to be in contact with a biological sample" as claimed. Ex. 1003, ¶ 127.

(2) "wherein the electrochemical glucose sensor comprises a first electrode, a second electrode, and an enzyme-containing film"

Berner describes a "biosensor" or "biosensor device" that includes multiple electrodes, such as a working electrode (or sensing electrode), a reference electrode, and a counter electrode:

> "***A 'biosensor' or 'biosensor device' includes, but is not limited to, a 'sensor element' which includes, but is not limited to, a 'biosensor electrode' or 'sensing electrode' or 'working electrode' which refers to the electrode that is monitored to determine the amount of electrical signal at a point in time or over a given time period, which signal is then correlated with the concentration of a chemical compound.*** The sensing electrode comprises a reactive surface which converts the analyte, or a derivative thereof, to electrical signal …
>
> ***The 'sensor element' can include components in addition to a biosensor electrode, for example, it can include a 'reference electrode,' and a 'counter electrode.'*** The term 'reference electrode' is used herein to mean an electrode that provides a reference potential, e.g., a potential can be established between a reference electrode and a working electrode. The term 'counter electrode' is used herein to mean an electrode in an electrochemical circuit which acts as a current source or sink to complete the electrochemical circuit … separate electrodes functioning as counter and reference electrodes are most

preferred."

Berner, 7:66-8:36 (emphasis added). Ex. 1003, ¶ 128.

Exemplary electrodes are shown in Berner's drawings, FIGS. 1A-1B:

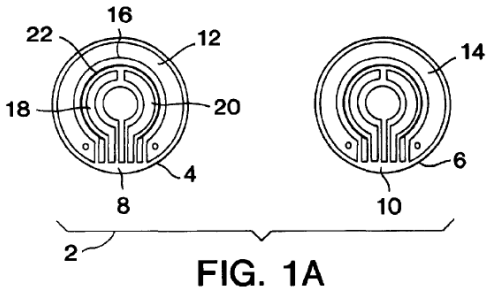

FIG. 1A

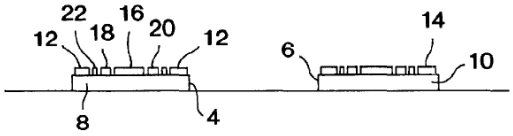

FIG. 1B

See also Berner, 15:9-15 (describing three biosensor electrodes including a working electrode 16, a reference electrode 18, and a counter electrode 20 shown in FIGs. 1A-1B). Ex. 1003, ¶¶ 129-130.

Similarly, FIG. 4 shows, among other things, "bimodal electrodes 40 and 41; sensing electrodes 42 and 43; reference electrodes 44 and 45" (Berner, 5:4-10):

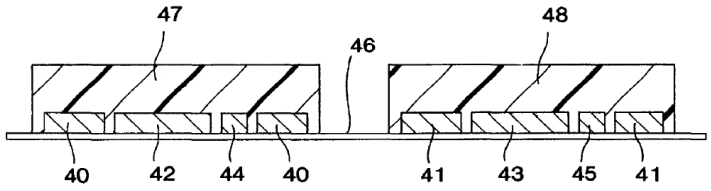

FIG. 4

In addition to the multiple electrodes, which comprise "a first electrode" and

"a second electrode," Berner also teaches or suggests "an enzyme-containing film." For example, Berner describes providing glucose oxidase as an enzyme in one or more "collection reservoirs." Berner, 10:58-11:11 ("In order to facilitate detection of the analyte, ***an enzyme can be disposed in the collection reservoir***, or, if several collection reservoirs are used, ***the enzyme can be disposed in several or all of the reservoirs*** … ***A suitable enzyme is glucose oxidase which oxidizes glucose to gluconic acid and hydrogen peroxide*** …") (emphasis added). Ex. 1003, ¶¶ 132-133.

Berner also teaches that the collection reservoirs (or "collection inserts") "can be ***in the form of a hydrogel*** (for example, ***in the shape of a disk or pad***)." Berner, 8:61-9:2 (emphasis added). *See also id*., 6:26-35. Berner's hydrogel collection inserts contain glucose oxidase enzyme. *See id*., 14:18-24 ("These sampling (extraction) and sensing operations are integrated such that ***glucose is extracted into the hydrogel collection pad where it contacts the GOx enzyme***."); 17:23-27 ("The electrode described is particularly adapted for use in conjunction with ***a hydrogel collection reservoir system for monitoring glucose levels*** in a subject through the reaction of collected glucose ***with the enzyme glucose oxidase present in the hydrogel matrix***.") (emphasis added). Ex. 1003, ¶¶ 134-135.

Berner further characterizes the hydrogel "collection insert" as one of several *layers* in a "collection assembly":

> "A 'collection assembly', as used herein, refers to ***structures comprised of several layers***, where the assembly includes at least one ***collection insert, for example a hydrogel***. An example of a collection assembly of the present invention is a mask layer, ***collection inserts***, and a retaining layer where the ***layers*** are held in appropriate, functional relationship to each other but are not necessarily a laminate, i.e., the layers may not be bonded together. The layers may, for example, be held together by interlocking geometry or friction."

Berner, 9:34-43 (emphasis added). Ex. 1003, ¶ 136.

Given the small dimensions of the collection reservoir(s) or collection insert(s), it would have been apparent to a POSITA that the disk- or pad-shaped hydrogel containing the enzyme must be in the form of *a thin layer*. Furthermore, the enzyme-containing hydrogel pads are shown as thin layers in Berner, FIG. 1B (hydrogel pads 8, 10); FIG. 4 (hydrogel pads 47, 48):

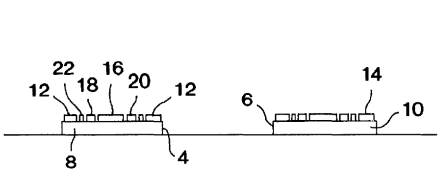

FIG. 1B

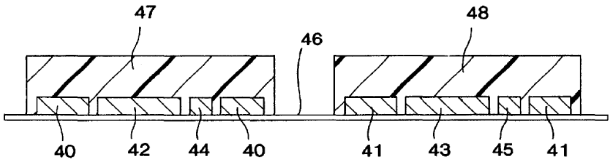

FIG. 4

Ex. 1003, ¶ 137.

Patent Owner argued, during the ITC proceeding, that the plain and ordinary meaning of "film" is "thin layer," and that the plain and ordinary meaning of an "enzyme-containing film" is a "thin layer that includes an enzyme." Ex. 1017

(Dexcom's Petition for Review of ID), 41-42, 50; Ex. 1003, ¶ 138.

Therefore, Berner teaches, or at least suggests, that its enzyme-containing hydrogel pad is a "thin layer that includes an enzyme"—an "enzyme-containing film" as claimed. Ex. 1003, ¶ 139.

As Dr. Smith explains, a POSITA would have understood that, for a biosensor in continual or continuous contact with the biological system or extracted samples, it would have been desirable, if not critical, to immobilize the glucose enzyme in a film or membrane structure. Ex. 1003, ¶ 140. Indeed, Berner incorporates by reference[4] two articles which describe enzymes immobilized with thin layers of membranes. *See* Ex. 1003, ¶ 141, citing Newman (Ex. 1018), p. 4595 (disclosing the fabrication and testing of an "enzyme electrode" having a thin layer of membrane containing glucose oxidase) and Updike (Ex. 1019), p. 986 (disclosing "immobilizing the enzyme glucose oxidase in a layer of acrylamide gel 25-50μ thick over the oxygen electrode").

Therefore, Berner discloses, teaches or suggests Element [16.a] as claimed. Ex. 1003, ¶ 142.

iii. Berner discloses "sensor electronics comprising a processor for executing a computer program code stored in a

[4] Berner explicitly incorporates by reference "[a]ll publications, patents and patent applications cited herein." Berner, 5:32-34.

memory to cause the sensor electronics to [perform the recited functions].” (Element [16.b]).

Berner discloses “sensor electronics comprising a processor”:

> “A ‘housing’ for the sampling system can further include ***suitable <u>electronics</u> (e.g., <u>microprocessor</u>, memory, display and other circuit components) and power sources for operating the sampling system in an automatic fashion***.
>
> A ‘monitoring system,’ as used herein, refers to a system useful for continually or continuously measuring a physiological analyte present in a biological system. Such a system typically includes, but is not limited to, sampling means, sensing means, and ***<u>a microprocessor means</u>*** in operative communication with the sampling means and the sensing means.”

Berner, 6:40-50 (emphasis added). Ex. 1003, ¶ 143.

In particular, Berner teaches that the “general methods (Steps A through F)” which are “each independently useful in analyte sensing systems” can be “carried out using ***a microprocessor*** in a monitoring system.” Berner, 13:2-16 (emphasis added). *See also id*., 15:67-16:3 (“The wristwatch [*i.e.*, GlucoWatch™] housing can further include ***suitable <u>electronics</u> (e.g., <u>microprocessor</u>, memory, display and other circuit components)*** and power sources for operating the automatic sampling system.”) (emphasis added). Ex. 1003, ¶ 144.

Berner further teaches that the microprocessor is used “for executing a

computer program code stored in a memory to cause the sensor electronics to [perform the recited functions]":

> "***The microprocessor generally uses a series of program sequences to control the operations of the sampling device, which program sequences can be stored in the microprocessor's read only memory (ROM). Embedded software (firmware)*** controls activation of measurement and display operations, calibration of analyte readings, setting and display of high and low analyte value alarms, display and setting of time and date functions, alarm time, and display of stored readings. Sensor signals obtained from the sensor electrodes are processed before storage and display by one or more ***signal processing functions or algorithms*** which are described in detail below. ***The microprocessor can also include an electronically erasable, programmable, read only memory (EEPROM)*** for storing calibration parameters (as described in detail below), user settings and all downloadable sequences."

Berner, 19:15-30 (emphasis added). *See also id*., 16:39-46 ("***Operation of the iontophoretic sampling device 30 is controlled by a controller 36 (e.g., a microprocessor)***, which interfaces with the iontophoretic electrodes, the sensor electrodes, the power supply, the optional temperature and/or conductance sensing elements, a display and other ***electronics***. For example, ***the controller 36 can include a programmable [] controlled circuit source/sink drive*** for driving the

iontophoretic electrodes.") (emphasis added). Ex. 1003, ¶ 145.

Therefore, Berner discloses Element [16.b] as claimed. Ex. 1003, ¶ 146.

iv. Berner discloses "apply a voltage to the electrochemical glucose sensor at a first setting" (Element [16.c]).

The claim limitation "apply a voltage to the electrochemical glucose sensor at a first setting" was construed as "put to use a voltage to the electrochemical glucose sensor at a first specified condition." Ex. 1016 at 24.

In Berner's glucose sensor system, voltages are put to use in two phases:

> "The general operation of an iontophoretic sampling system is the cyclical repetition of two phases: (1) a reverse-iontophoretic phase, followed by a (2) sensing phase. ***During the reverse iontophoretic phase, the first bimodal electrode (FIGS. 4, 40) acts as an iontophoretic cathode and the second bimodal electrode (FIGS. 4, 41) acts as an iontophoretic anode to complete the circuit.*** Analyte is collected in the reservoirs, for example, a hydrogel (FIGS. 4, 47 and 48). At the end of the reverse iontophoretic phase, the iontophoretic current is turned off. ***During the sensing phase, in the case of glucose, a potential is applied between the reference electrode (FIGS. 4, 44) and the sensing electrode (FIGS. 4, 42).***"

Berner, 17:6-18 (emphasis added). Ex. 1003, ¶ 147.

Of particular relevance to Element [16.c] is the application of one or more voltages in the reverse-iontophoretic phase. Berner explains that "iontophoresis"

refers to "a method for transporting substances across tissue ***by way of an application of electrical energy to the tissue***" which "can be carried out using standard methods known to those of skill in the art, for example, by ***establishing an electrical potential using a direct current (DC) between fixed anode and cathode 'iontophoretic electrodes,'*** ..." Berner, 7:26-39 (emphasis added). Ex. 1003, ¶ 148.

Specifically, Berner teaches applying a voltage between the iontophoretic electrodes of a biosensor (*i.e.*, "the electrochemical glucose sensor") to extract substances including an analyte of interest (*e.g.*, glucose) into collection reservoir(s):

> "In use, ***an electric potential (either direct current or a more complex waveform) is applied between the two iontophoretic electrodes 12 and 14*** such that current flows from the first iontophoretic electrode 12, through the first conductive medium 8 into the skin or mucosal surface, and then back out through the second conductive medium 10 to the second iontophoretic electrode 14. ***The current flow is sufficient to extract substances including an analyte of interest through the skin into one or both of collection reservoirs 4 and 6.***"

Berner, 16:7-18 (emphasis added). Ex. 1003, ¶ 149.

A POSITA would have understood that, to the extent "a more complex waveform" of electric potential, as opposed to a direct current (DC) potential, is

applied to the iontophoretic electrodes, the voltage put to use at the biosensor ("the electrochemical glucose sensor") would vary over time: at one moment the voltage would be at a first specified condition (or "a first setting"), and at a subsequent moment the voltage would be at a second specified condition (or "a different setting"). This is referred to as "Case 1" in the following subsections of this Petition. Ex. 1003, ¶ 150.

Additionally or alternatively, a POSITA would have understood that the application of an electric potential to the iontophoretic electrodes during Berner's reverse-iontophoretic phase, as opposed to applying a potential to the sensing electrodes during the subsequent sensing phase, also constitutes a first specified condition (or "a first setting") at which the voltage is put to use at the biosensor ("the electrochemical glucose sensor"). This is referred to as "Case 2" in following subsections of this Petition. Ex. 1003, ¶ 151.

Thus, in either Case 1 or Case 2, Berner teaches "apply a voltage to the electrochemical glucose sensor at a first setting." Therefore, Berner discloses Element [16.c] as claimed. Ex. 1003, ¶¶ 152-153.

v. Berner discloses "switch the voltage applied to the electrochemical sensor to a different setting" (Element [16.d]).

The claim limitation "switch the voltage applied to the electrochemical sensor to a different setting" was construed as "change the voltage that was put to

use at the electrochemical glucose sensor to a different specified condition." Ex. 1016 at 30.

Case 1. Switch the voltage setting applied to the iontophoretic electrodes

As explained above, Berner teaches that, during reverse-iontophoretic phase, "an electric potential (either direct current or ***a more complex waveform***) is applied between the two iontophoretic electrodes 12 and 14 ..." Berner, 16:10-18 (emphasis added). As explained above with respect to Case 1, an electric potential with "a more complex waveform" than a DC waveform must have a voltage value which varies with time, resulting in "a first setting" (*e.g.*, a first value) at a first moment and then "a different setting" at a subsequent moment. Ex. 1003, ¶ 154.

As one particular example of the "more complex waveform," Berner describes alternating the polarity of the voltage applied to the iontophoretic electrodes:

> "***The electric potential may be applied using any suitable technique***, for example, the applied current density may be in the range of about 0.01 to 0.5 mA/cm^2. In a preferred embodiment, the device is used for continual or continuous monitoring, and ***the polarity of iontophoretic electrodes 12 and 14 is alternated at a rate of about one switch every 10 seconds to about one switch every hour*** so that each electrode is alternately a cathode or an anode."

Berner, 16:18-26 (emphasis added). Thus, when the voltage between the iontophoretic electrodes has a first polarity, the applied voltage is at "a first setting"; when the voltage between the iontophoretic electrodes has a second polarity (*e.g.*, being reversed with respect to the first polarity), the applied voltage has been switched to "a different setting." Ex. 1003, ¶ 155.

Therefore, in Case 1, Berner discloses "switch the voltage applied to the electrochemical sensor [from a first setting] to a different setting." Ex. 1003, ¶ 156.

Case 2. Switch settings from reverse-iontophoretic phase to sensing phase

Berner also teaches applying a voltage to a set of sensor electrodes (or "sensing electrodes") when the biosensor switches from reverse-iontophoretic phase to sensing phase:

> "At the end of the reverse iontophoretic phase, the iontophoretic current is turned off. ***During the sensing phase, in the case of glucose, a potential is applied between the reference electrode (FIGS. 4, 44) and the sensing electrode (FIGS. 4, 42).*** The chemical signal reacts catalytically on the catalytic face of the first sensing electrode (FIGS. 4, 42) producing an electrical current, while the first bi-modal electrode (FIGS. 4, 40) acts as a counter electrode to complete the electrical circuit." Berner, 17:14-22 (emphasis added).

See also id., 16:36-38, 17:58-67. Ex. 1003, ¶ 157.

Since at least some of the sensing electrodes are different from the set of iontophoretic electrodes, the voltage put to use during the sensing phase has a specified condition or "setting" (*i.e.*, where or across which electrodes to apply the voltage) that is different from the voltage that is put to use during the reverse-iontophoretic phase. Thus, in Case 2, Berner also teaches "switch the voltage applied to the electrochemical sensor [from a first setting] to a different setting." Ex. 1003, ¶ 158.

Therefore, in both Case 1 and Case 2, Berner discloses Element [16.d] as claimed. Ex. 1003, ¶ 159.

vi. Berner discloses "measure a signal response of the electrochemical glucose sensor responsive to the switching" (Element [16.e]).

<u>Raw electrical signal as "*signal response*" (in Cases 1 & 2)</u>

Whether the "switching" refers to the switching of the voltage applied between the iontophoretic electrodes (*e.g.*, based on a "complex waveform") within reverse-iontophoretic phase (Case 1) or the switching of voltage settings from reverse-iontophoretic phase to sensing phase (Case 2), an ultimate goal (and the result) is the measurement of a raw electrical signal based on the electrochemical reaction of the extracted sample with a glucose enzyme:

> "These sampling (extraction) and sensing operations are integrated such that glucose is extracted into the hydrogel collection pad where it contacts the GOx enzyme. The GOx

> enzyme converts glucose and oxygen in the hydrogel to hydrogen peroxide which diffuses to the sensor and is catalyzed by the sensor to regenerate oxygen and form electrons. ***The electrons generate <u>an electrical signal that can be measured</u>, analyzed, and correlated to blood glucose.***" Berner, 14:18-25 (emphasis added).
>
> "During the sensing phase, in the case of glucose, a potential is applied between the reference electrode (FIGS. 4, 44) and the sensing electrode (FIGS. 4, 42). ***The chemical signal reacts catalytically on the catalytic face of the first sensing electrode (FIGS. 4, 42) <u>producing an electrical current</u>***, while the first bi-modal electrode (FIGS. 4, 40) acts as a counter electrode to complete the electrical circuit." Berner, 17:15-22 (emphasis added).

See also id., 20:47-21:2 (measuring "the electrochemical signal" or "raw signal" or "sensor reading" during each sensing cycle as a signal response); 21:10-36 (measuring "the peak of a sensor reading," "anodal points," or "background current" as signal responses). Ex. 1003, ¶ 160.

Since the raw, glucose-indicating signal (*e.g.*, the electrical current or "electrochemical signal" from the sensing electrode, the "sensor reading" of raw signal) would not have been available but for the switching of the voltage applied between the iontophoretic electrodes (*e.g.*, based on a "complex waveform") within reverse-iontophoretic phase and the switching of voltage settings from

reverse-iontophoretic phase to sensing phase, a POSITA would have understood that the measurement of the raw signal from Berner's biosensor is indirectly or directly "responsive to the switching" as claimed. Ex. 1003, ¶ 161.

Therefore, Berner discloses measuring the raw electrical signal as "a signal response of the electrochemical glucose sensor responsive to the switching." Ex. 1003, ¶ 162.

"System voltage" or "iontophoresis voltage" as "*signal response*" (in Case 1)

Berner also teaches measuring various voltage signals during iontophoretic sampling (*i.e.*, reverse-iontophoretic phase). Ex. 1003, ¶ 163.

For example, Berner describes a data screening method involving assessing a "system voltage" during iontophoretic sampling:

> "Yet further data screens which are used in the practice of the invention take into consideration the expected behavior of the sampling/sensing device. ***In iontophoretic sampling***, for example, there is ***a skin equilibration period*** before which measurements will generally be less accurate. ***During this equilibration period, the system voltage can be assessed and compared against an objective high voltage threshold.*** If this high voltage limit is exceeded, a data screen is used to exclude the corresponding analyte measurement, since the iontophoretic current was not at a target value due to high skin resistance (as indicted by the high voltage level)."

Berner, 20:36-46 (emphasis added). Because the system voltage is assessed during

iontophoretic sampling—in "a skin equilibration period before which measurements will generally be less accurate"—a POSITA would have understood that the system voltage is measured after, and in response to, the iontophoretic extraction of glucose which, as described above, may be based on "switching" (with a complex waveform) the electric potential applied between the two iontophoretic electrodes (*see* Berner, 16:7-18). Thus, the system voltage is "a signal response of the electrochemical glucose sensor responsive to the switching" in Case 1. Ex. 1003, ¶¶ 164-165.

Similarly, Berner describes another data screening method involving "iontophoresis voltages":

> "(iv) voltage--Voltage Stability. If the glucose monitoring device is mechanically disturbed, there can be a larger change (e.g., larger relative to when the monitor is functioning under normal conditions) in ***iontophoresis voltage***. This could lead to an aberrant reading. ***If the percentage difference between successive cathodal or anodal iontophoresis voltages is gr[e]ater than a predetermined value, for example, 15%, then an error is indicated.***"

Berner, 21:37-44 (emphasis added). Ex. 1003, ¶ 166.

In the context of the above-quoted passage, a POSITA would have understood that the iontophoresis voltage is another "signal response" of Berner's biosensor in response to the iontophoretic extraction process which may be based

on "switching" (with a complex waveform) the electric potential applied to the iontophoretic electrodes (*see* Berner, 16:7-18). Ex. 1003, ¶ 167.

Therefore, Berner discloses Element [16.e] as claimed. Ex. 1003, ¶ 168.

> ***vii. Berner discloses "evaluate a severity associated with a signal artifact based on the measured signal response of the electrochemical glucose sensor to the switching, wherein the signal artifact is associated with a non-glucose rate limiting phenomenon" (Element [16.f]).***

Berner disclose a number of data screening methods which "evaluate a severity associated with a signal artifact based on the measured signal response …" as claimed. Ex. 1003, ¶ 169.

Raw electrical signal as "*signal response*" (in Cases 1 & 2)

When the raw electrical signal is the "signal response," Berner teaches "monitoring signal behavior during sensing operations" and/or comparing the sensor reading of the raw signal against "raw signal thresholds" to evaluate the severity of signal artifacts:

> "In addition, ***the electrochemical signal during each sensing cycle*** is expected to behave as a smooth, monotonically decreasing signal which represents depletion of the hydrogen peroxide by the sensor electrode. ***Significant departure from this expected behavior is indicative of a poor or incorrect measurement (e.g., a non-monotonically decreasing signal is indicative of excessive noise in the biosensor signal), and thus monitoring signal behavior during sensing operations***

> ***provides yet a further data screen for invalidating or correcting measurements.***
>
> ***Raw signal thresholds can also be used in the data screening method of the present invention.*** For example, any sensor reading that is less than some minimum threshold can indicate that the sampling/sensing device is not operating correctly, for example, where the biosensor electrode is disconnected. In addition, any chemical sensor will have a maximum range in which the device can operate reliably. A reading greater than some maximal value, then, indicates that the measurement is off-scale, and thus possibly invalid. Accordingly, minimum and maximum signal thresholds are used herein as data screens to invalidate or correct measurements."

Berner, 20:47-21:1 (emphasis added). Ex. 1003, ¶ 170.

The behavior of the raw electrical signal as compared to its "expected behavior" reflects the severity of a "signal artifact" (*i.e.*, "a particular type of noise" or "an artifact relating to signal noise") because "[s]ignificant departure from this expected behavior is indicative of a poor or incorrect measurement (e.g., a non-monotonically decreasing signal is indicative of ***excessive noise in the biosensor signal***)." Berner, 20:47-56 (emphasis added). In addition, a POSITA would have understood that a non-monotonically decreasing signal also marks a significant deviation from the well-known Cottrell curve and therefore indicates interferences ("artifacts") from conditions unrelated to the glucose concentration in the extracted

sample, and thus related to a non-glucose rate limiting phenomenon. Ex. 1003, ¶¶ 171-172.

Thus, monitoring the signal behavior, as taught by Berner, can "evaluate a severity associated with a signal artifact based on the measured signal response of the electrochemical glucose sensor to the switching, wherein the signal artifact is associated with a non-glucose rate limiting phenomenon." Ex. 1003, ¶ 173.

Similarly, the measured values of the raw electrical signal as compared to its predetermined minimum and/or maximum thresholds can also indicate that "the sampling/sensing device is not operating correctly" (*e.g.*, disconnected) or that "the measurement is off-scale, and thus possibly invalid." A POSITA would have understood that such excessively high or low readings of the raw signal are also artifacts (or the result of signal noises) unrelated to the glucose concentration in the extracted sample—a "signal artifact" that is "associated with a non-glucose rate limiting phenomenon." Ex. 1003, ¶ 174.

Thus, assessing the signal values can also "evaluate a severity associated with a signal artifact based on the measured signal response of the electrochemical glucose sensor to the switching, wherein the signal artifact is associated with a non-glucose rate limiting phenomenon." Ex. 1003, ¶ 175.

"System voltage" or "iontophoresis voltage" as "*signal response*" (in Case 1)

When the "system voltage" or "iontophoresis voltage" is the "signal

response," Berner similarly teaches assessing these voltages against predetermined thresholds to "evaluate a severity associated with a signal artifact":

> "***During this equilibration period, the system voltage can be assessed and compared against an objective high voltage threshold.*** If this high voltage limit is exceeded, a data screen is used to exclude the corresponding analyte measurement, since the iontophoretic current was not at a target value ***due to high skin resistance (as indicted by the high voltage level)***." Berner, 20:40-46 (emphasis added).
>
> "(iv) voltage--Voltage Stability. ***If the glucose monitoring device is mechanically disturbed***, there can be a larger change (e.g., larger relative to when the monitor is functioning under normal conditions) in iontophoresis voltage. This could lead to an aberrant reading. ***If the percentage difference between successive cathodal or anodal iontophoresis voltages is gr[e]ater than a predetermined value, for example, 15%, then an error is indicated.***" Berner, 21:37-44 (emphasis added).

Ex. 1003, ¶ 176.

In these two data screens, the severity of the signal artifacts is evaluated based on a comparison between "the system voltage" and "an objective high voltage threshold" or a comparison between "the percentage difference between successive cathodal or anodal iontophoresis voltages" and "a predetermined value." And, the signal artifacts are related to "high skin resistance" and

mechanical disturbance respectively, both of which are conditions unrelated to the glucose concentration in the extracted sample. Ex. 1003, ¶ 177.

Thus, through these data screens, Berner teaches "evaluate a severity associated with a signal artifact based on the measured signal response of the electrochemical glucose sensor to the switching, wherein the signal artifact is associated with a non-glucose rate limiting phenomenon." Ex. 1003, ¶ 178.

Therefore, Berner discloses Element [16.f] as claimed. Ex. 1003, ¶ 179.

viii. Berner discloses "generate an estimated glucose concentration value when the severity associated with the signal artifact is evaluated to be under a predetermined threshold, wherein the estimated glucose concentration value accounts for the severity associated with the signal artifact" (Element [16.g]).

(1) "generate an estimated glucose concentration value when the severity associated with the signal artifact is evaluated to be under a predetermined threshold"

Berner teaches screening biosensor signals to eliminate poor or incorrect signals with "a predefined set of selection criteria," such that only trustworthy glucose concentration values would be retained and displayed:

> "More particularly, ***the raw signals undergo a data screening method in order to eliminate outlier signals and/or poor (incorrect) signals*** using ***a predefined set of selection criteria***." Berner, 3:23-26 (emphasis added).
>
> "The raw signal obtained from the above-described glucose

> monitoring device can be screened to detect deviations from expected behavior which are indicative of poor or incorrect signals that will not correlate with blood glucose. Signals that are identified as poor or incorrect in this data screen may be discarded or otherwise corrected for prior to any signal processing and/or conversion in order to maintain data integrity. In the method of the invention, ***an objective set of selection criteria is established which can then be used to accept or discard signals from the sensing device***." Berner, 19:33-42 (emphasis added).

Ex. 1003, ¶ 180.

During data screening, "the severity associated with the signal artifact" is evaluated against "a predetermined threshold" as claimed. For example, as described above, with the raw electrical signal as the "signal response," its measured value is compared to its predetermined minimum and/or maximum thresholds; and the signal behavior is monitored for any "significant departure" from the "expected behavior" which procedure, as performed by a microprocessor or controller, also implicitly involves "a predetermined threshold" (*e.g.*, to quantify the extent of deviation from the expected behavior such as the Cottrell curve). *See* Berner, 20:47-21:1. Ex. 1003, ¶ 181.

Similarly, with the "system voltage" as the "signal response," the "objective high voltage threshold" constitutes "a predetermined threshold" for the severity;

and, with the "iontophoresis voltage" as the "signal response," the "predetermined value" with which "the percentage difference between successive cathodal or anodal iontophoresis voltages" is compared constitutes "a predetermined threshold." *See* Berner, 20:40-46, 21:37-44. Ex. 1003, ¶ 182.

In each of these data screens, the raw signal is validated or accepted only if the "severity" is under the "predetermined threshold" as claimed. For example, for the raw signal to be considered reliable, the sensor reading should be no greater than "the maximum value," the signal behavior must be sufficiently close to the "expected behavior" (*i.e.*, the difference being small enough); the system voltage cannot exceed the "objective high voltage threshold," and "the percentage difference between successive cathodal or anodal iontophoresis voltages" not to be greater than "a predetermined value, for example, 15%." *See* Berner, 20:36-21:1, 21:37-44. Ex. 1003, ¶ 183.

The screened raw signal, if validated and accepted, could then be used to "generate an estimated glucose concentration value":

> "Continuing with the method of the invention, ***any of the raw signals obtained from Step A, the screened raw signal obtained from Step B***, or the initial output signal obtained from Step C (or from Steps B and C), ***can be converted into an analyte-specific value using a calibration step which correlates the signal obtained from the sensing device with the concentration of the analyte present in the biological system***.

> A wide variety of calibration techniques can be used to interpret such signals … ***One method of calibration involves estimation techniques.***"

Berner, 27:66-28:15 (emphasis added); *see also id*., 12:24-28. Or, a poor or incorrect signal "otherwise corrected for" would be understood by a POSITA to represent "an estimated glucose concentration value." Ex. 1003, ¶¶ 184-185.

Therefore, Berner discloses "generate an estimated glucose concentration value when the severity associated with the signal artifact is evaluated to be under a predetermined threshold." Ex. 1003, ¶ 186.

(2) "wherein the estimated glucose concentration value accounts for the severity associated with the signal artifact"

The claim limitation "wherein the estimated glucose concentration value accounts for the severity associated with the signal artifact" was construed to mean "wherein the degree of the signal artifact is taken into account in the estimated glucose concentration value." Ex. 1016 at 40.

Berner teaches or suggests at least two ways by which the severity of the signal artifact is taken into account in the estimated glucose concentration value. Ex. 1003, ¶ 187.

First, under Patent Owner's position, as discussed below, by performing the above-described data screens *before* calculating the estimated glucose concentration, Berner's biosensor takes into account the degree of severity of any

signal artifact associated with those data screens. The biosensor system would not proceed to compute the glucose value at all if that severity is above the predetermined threshold; in other words, the estimated glucose concentration value, if generated, indicates the severity is low enough and thereby "accounts for the severity associated with the signal artifact." Ex. 1003, ¶¶ 188-189.

Notably, Patent Owner has taken this position in the related ITC proceeding, arguing that the severity of a signal artifact used to screen glucose measurements is effectively taken into account in a validated glucose concentration value:

> "By performing this partial fill check before calculating the estimated glucose concentration [Glucose], the AgaMatrix system takes into account or considers the degree of severity of any signal artifact associated with the available electrode surface area. If that severity is below a certain threshold, that is to say the capacitance is above a set level, then the algorithm permits the system to compute the glucose estimate [Glucose]."

Ex. 1020 (Dexcom's Infringement Expert Report), ¶ 627.

Second, apart from data screening, Berner also teaches that the screened or unscreened raw signals "can be entered directly into a conversion step to obtain an initial signal output which is indicative of the amount of analyte extracted by the sampling system" (Berner, 21:60-22:2) and/or "converted into an analyte-specific value using a calibration step" (*id*., 27:66-28:6). The resulting glucose concentration value can take into account (*e.g.*, by reducing or eliminating) various

signal artifacts to the extent they are in an unscreened raw signal or they are not severe enough to cause a screened raw signal to be discarded. Ex. 1003, ¶ 190.

For example, Berner teaches a signal conversion technique by which a "background signal value is subtracted from an actual signal measurement value (which includes both analyte-specific and background components) ***to obtain a corrected measurement value***." *See* Berner, 22:5-62 (emphasis added). Berner further teaches using the conversion step to "***correct for changing conditions in the biological system and/or the biosensor system*** (e.g., temperature fluctuations in the biological system, temperature fluctuations in the biosensor element, or combinations thereof)" because "[t]emperature can affect the signal in a number of ways, such as by changing background, reaction constants, and/or diffusion coefficients" *Id*., 22:65-23:4 (emphasis added). Berner describes calculating a "temperature corrected baseline current" in particular to remove interferences from temperature. *See id*., 23:33-59. Ex. 1003, ¶ 191.

Thus, a POSITA would have understood that the estimated glucose concentration value created from Berner's conversion step takes into account, either explicitly or implicitly, the severity of various signal artifacts. For example, by subtracting the "temperature corrected baseline current," the final glucose value explicitly accounts for the severity of temperature-related signal artifacts. By correcting for "changing conditions in the biological system and/or the biosensor

system," Berner also implicitly teaches accounting for the severity of signal artifacts, including but not limited to those related to excessive noise, electrode disconnection, high skin resistance, and mechanical disturbance of the sensor as described above. *See* Berner, 20:36-21:1, 21:37-44. Ex. 1003, ¶ 192.

Therefore, Berner discloses Element [16.g] as claimed. Ex. 1003, ¶ 193.

ix. Berner discloses "a user interface configured to display the estimated glucose concentration value" (Element [16.h]).

Berner discloses that "an optional liquid crystal display (LCD) can provide visual prompts, readouts and visual alarm indications" for the biosensor device. Berner, 19:12-14. Such a LCD display of "readouts" refers to the display of estimated glucose concentration value. Ex. 1003, ¶ 194.

For example, Berner explicitly incorporates by reference PCT International Publication No. WO 96/00110 ("Tamada," Ex. 1021) because it discloses the details of the electrode assemblies and devices for iontophoretic extraction of glucose employed by Berner's biosensor. Berner, 14:64-15:2. Berner further teaches that "[t]he components described herein are intended for use in a[n] automatic sampling device which is configured to be worn like an ordinary wristwatch" such as what is described in "International Publication No. WO 96/00110, published Jan. 4, 1996." Berner, 15:58-16:3. Ex. 1003, ¶ 195.

Tamada discloses:

> "Preferably, a sensor selected to sense the presence, and

possibly the level, of a target substance within a reservoir is in contact with the reservoir. ***A display communicating with the sensor provides an indication of the presence and (possibly) the level of the target substance within the reservoir.*** If suitably calibrated, ***the display can indicate concentration of the target substance within the subject's blood***." Tamada, 22:25-31 (emphasis added).

"The ***display*** may be used, for example, ***to allow patients to scroll through their present and previous analyte (e.g., glucose) level readings*** and to alert patients to fluctuations in their levels." Tamada, 30:15-18 (emphasis added).

See also Tamada, 31:25-31 ("The current provides a signal that is interpreted by the system controller to ***provide a glucose concentration value for display***. This current may be correlated with the subject's blood glucose concentration so that ***the system displays the subject's actual blood glucose concentration as measured by the iontophoretic collection system***.") (emphasis added). Ex. 1003, ¶ 196.

Thus, at least by incorporating Tamada's disclosure of displaying glucose concentration values, Berner discloses "a user interface configured to display the estimated glucose concentration value." Ex. 1003, ¶ 197

Therefore, Berner discloses Element [16.h] as claimed. Ex. 1003, ¶ 198.

Since Berner discloses, teaches, or suggests all the elements of claim 16, Berner renders this claim obvious. Ex. 1003, ¶ 199.

2. Dependent Claim 17

Dependent claim 17 incorporates the limitations of independent claim 16 (which are all disclosed, taught or suggested by Berner) and additionally recites "*wherein the biological sample is blood*."

Berner identifies "monitoring *blood* glucose concentrations" as "one important application of the invention" (Berner, 1:14-20) and further states:

> "***The raw signal can be obtained using any suitable sensing methodology including***, for example, ***methods which rely on direct contact of a sensing apparatus with the biological system***; ***methods which extract samples from the biological system by invasive***, minimally invasive, and non-invasive ***sampling techniques, wherein the sensing apparatus is contacted with the extracted sample***; methods which rely on indirect contact of a sensing apparatus with the biological system; and the like."

Berner, 2:43-51 (emphasis added). *See also id*., 11:45-53. Ex. 1003, ¶ 201.

As one example, Berner teaches that "the methods of the present invention include enhancement of skin permeability by pricking the skin with micro-needles" (Berner, 4:7-11) and notes in particular that "[t]hese [transdermal extraction] methods can, of course, be coupled with application of skin penetration enhancers or skin permeability enhancing technique such as tape stripping or pricking with micro-needles" (*id*., 7:12-25). It was well known, and a POSITA would have

understood, that pricking the skin with micro-needles (as that term is understood in this context) would be expected to produce a sample of blood with which Berner's sensor will come into contact. Ex. 1003, ¶¶ 202-203.

For example, Leong (Ex. 1022) discloses "percutaneous biological fluid sampling and analyte measurement" employing micro-needles having "lengths and sizes within certain ranges depending on the type of biological fluid (e.g., interstitial fluid, ***blood***, or both) desired for sampling and the thickness of the skin layers of the particular patient being tested." Leong, 1:7-10, 8:58-63 (emphasis added). *See also* Whitson (Ex. 1023), 2:12-21, FIGs. 3-8 (disclosing a test strip comprising an array of microneedles each being "adapted to puncture skin and ***to draw blood***" for glucose monitoring). *See also* Berner, 6:23-25 (disclosing (blood) sample extraction with "traditional needle and syringe"). Ex. 1003, ¶¶ 204-205.

A POSITA would have understood that extracted blood samples could be the subject of continuous glucose measurement so long as a membrane is used to prevent catalase in the blood samples from entering the collection reservoir. Ex. 1003, ¶ 206.

Thus, a POSITA would have understood Berner to teach, or at least suggest, extracting a sample of blood to measure its glucose concentration. Ex. 1003, ¶ 207.

Therefore, Berner teaches or suggests all the elements of claim 17 and

renders this claim obvious. Ex. 1003, ¶ 208.

3. Dependent Claim 18

Dependent claim 18 incorporates the limitations of independent claim 16 (which are all disclosed, taught or suggested by Berner) and additionally recites "*wherein measuring the signal response comprises measuring a current output of the electrochemical glucose sensor*."

As shown above in connection with Element [16.e], Berner discloses that "[t]he GOx enzyme converts glucose and oxygen in the hydrogel to hydrogen peroxide which diffuses to the sensor and is catalyzed by the sensor to regenerate oxygen and ***form electrons***" and that "***[t]he electrons generate an electrical signal that can be measured, analyzed, and correlated to blood glucose.***" Berner, 14:18-25 (emphasis added). Berner further teaches measuring "an electrical current" from "the catalytic face of the first sensing electrode (FIGS. 4, 42)." Berner, 17:15-22. A POSITA would have understood that such "an electrical current" constitutes "a current output" of Berner's biosensor ("the electrochemical glucose sensor"). Ex. 1003, ¶¶ 210-211.

Therefore, Berner discloses all the elements of claim 18 and renders this claim obvious. Ex. 1003, ¶ 212.

4. Dependent Claim 19

Dependent claim 19 incorporates the limitations of independent claim 16

(which are all disclosed, taught or suggested by Berner) and additionally recites "*wherein measuring the signal response comprises measuring a voltage output of the electrochemical glucose sensor*."

As shown above in connection with Element [16.e], Berner teaches measuring "system voltage" and/or "iontophoresis voltage" during iontophoretic sampling as signal responses. *See* Berner, 20:36-46, 21:37-44. A POSITA would have understood that either of these voltages is a "voltage output" from Berner's biosensor ("the electrochemical glucose sensor"). Ex. 1003, ¶¶ 214-215.

Therefore, Berner discloses all the elements of claim 19 and renders this claim obvious. Ex. 1003, ¶ 216.

5. Dependent Claim 20

Dependent claim 20 incorporates the limitations of independent claim 16 (which are all disclosed, taught or suggested by Berner) and additionally recites "*wherein the measured signal response is a voltage response of the electrochemical glucose sensor*."

As shown above in connection with Element [16.e] and claim 19, Berner teaches measuring "system voltage" and/or "iontophoresis voltage" during iontophoretic sampling as signal responses of the biosensor. *See* Berner, 20:36-46, 21:37-44. A POSITA would have understood that either of these voltages is a "voltage response" from Berner's biosensor ("the electrochemical glucose

sensor"). Ex. 1003, ¶¶ 218-219.

Therefore, Berner discloses all the elements of claim 20 and renders this claim obvious. Ex. 1003, ¶ 220.

6. Dependent Claim 21

Dependent claim 21 incorporates the limitations of independent claim 16 (which are all disclosed, taught or suggested by Berner) and additionally recites "*wherein the electrochemical glucose sensor is a continuous glucose sensor*."

As shown above in connection with Element [16.preamble], Berner's invention "relates generally to ***methods for continually or continuously measuring the concentration of target chemical analytes present in a biological system***" and "[o]ne important application of the invention involves ***a method for monitoring blood glucose concentrations***." Berner, 1:14-20 (emphasis added). *See also id*., Abstract. A POSITA would have understood that Berner's biosensor ("the electrochemical glucose sensor") is "a continuous glucose sensor." Ex. 1003, ¶¶ 222-223.

Therefore, Berner discloses all the elements of claim 21 and renders this claim obvious. Ex. 1003, ¶ 224.

7. Dependent Claim 23

Dependent claim 23 incorporates the limitations of independent claim 16 (which are all disclosed, taught or suggested by Berner) and additionally recites

"*wherein the non-glucose rate limiting phenomenon is associated with a temperature*."

As shown above in connection with Element [16.f], when the raw electrical signal is the "signal response" and it is compared with an "expected behavior" (*e.g.*, "a smooth, monotonic decreasing signal" (Berner 20:47-50)) or "raw signal thresholds" to evaluate the severity of signal artifacts therein, a POSITA would have understood that such signal artifacts could originate from a number of conditions, other than glucose, that affect an electrochemical reaction rate of the electrochemical glucose sensor. Ex. 1003, ¶ 226.

For example, Berner teaches using the conversion step "to correct for changing conditions in the biological system and/or the biosensor system (e.g., ***temperature*** fluctuations in the biological system, ***temperature*** fluctuations in the biosensor element, or combinations thereof)." Berner, 3:41-46 (emphasis added). Berner further discloses that "***[t]emperature*** can affect the signal in a number of ways, such as by changing background, reaction constants, and/or diffusion coefficients." *Id*., 23:2-4 (emphasis added). Ex. 1003, ¶ 227.

Berner specifically recognizes that the raw or screened raw signal need to be processed in the conversion step "in order to remove or correct for background information present in the signal" and that "[o]ne such background signal is the 'baseline background,' which, in the context of electrochemical detection, is ***a***

current (nA) generated by the sensing device independent of the presence or absence of the analyte of interest." Berner, 22:5-15 (emphasis added). "This baseline background interferes with measurement of analyte of interest, and the amount of baseline background can vary with time, ***temperature*** and other variable factors." *Id*., 22:15-18 (emphasis added). Ex. 1003, ¶¶ 228-229.

Thus, Berner teaches, or at least suggests, "wherein the non-glucose rate limiting phenomenon is associated with a temperature" and renders claim 23 obvious. Ex. 1003, ¶ 230.

8. Dependent Claim 24

Dependent claim 24 incorporates the limitations of independent claim 16 (which are all disclosed, taught or suggested by Berner) and additionally recites "*wherein the non-glucose rate limiting phenomenon is associated with an available electrode surface area*."

The claim term "available electrode surface area" was construed as "surface area of an electrode where an electrochemical reaction occurs."

As shown above in connection with Element [16.f] and claim 23, when the raw electrical signal is the "signal response" and it is compared with an "expected behavior" (*e.g.*, Cottrell curve) or "raw signal thresholds" to evaluate the severity of signal artifacts therein, such signal artifacts could originate from a number of conditions, other than glucose, that affect an electrochemical reaction rate of the

electrochemical glucose sensor. Ex. 1003, ¶ 232.

It is well known that the surface area of an electrode where an electrochemical reaction occurs (*i.e.*, the "available electrode surface area") is an important, non-glucose factor in amperometric measurement by an electrochemical glucose sensor. Ex. 1003, ¶ 233 (citing Ex. 1011, pp. 162-163). Indeed, Berner recognizes the significance of the electrode surface area in electrochemical glucose measurements. For example, in defining a "biosensor" or "biosensor device," Berner teaches that "[t]he sensing electrode comprises ***a reactive surface*** which converts the analyte, or a derivative thereof, to electrical signal." Berner, 8:6-8 (emphasis added). The "reactive surface" is defined as "the surface of the sensing electrode" that, among other things, "defines the ***electrode surface area*** that, when composed of a reactive material, is sufficient to drive the electrochemical reaction at a rate sufficient to generate a detectable, reproducibly measurable, electrical signal …" *Id*., 8:44-60 (emphasis added). Ex. 1003, ¶ 234.

It was also well known that these molecules and any products of the electrochemical reaction can accumulate on the electrode surface during the continuous use of the sensor, typically causing the electrode surface area available for electrochemical reaction to decrease over time, introducing measurement errors. *See* Ex. 1003, ¶ 235, citing Kurnik (Ex. 1025), 13:22-32 (describing "***accumulation of material on the face of the electrode subassembly***" in a glucose

sensor) (emphasis added).

In light of Berner's description of the electrode surface area and its well-known role in affecting Cottrell current, a POSITA would have understood "an available electrode surface area" to be a non-glucose rate limiting phenomenon that inevitably influences, and causes artifacts in, the raw signal (*i.e.*, "signal response") measured from the electrochemical glucose sensor. Ex. 1003, ¶ 236.

Thus, Berner teaches, or at least suggests, "wherein the non-glucose rate limiting phenomenon is associated with an available electrode surface area" and renders claim 24 obvious. Ex. 1003, ¶ 237.

9. Dependent Claim 25

Dependent claim 25 incorporates the limitations of independent claim 16 (which are all taught or suggested by Berner) and additionally recites "*wherein the non-glucose rate limiting phenomenon is associated with a biochemical species*."

As shown above in connection with Element [16.f] and claim 23, when the raw electrical signal is the "signal response," its associated signal artifacts could originate from a number of conditions, other than glucose, that affect an electrochemical reaction rate of the electrochemical glucose sensor. Ex. 1003, ¶ 239.

Berner teaches that "***electrochemically active interfering species*** [*e.g.*, bilirubin, dopamine, etc., extracted out of skin by the reverse iontophoresis] and/or

residual analyte can be present in the device which will further interfere with measurement of the analyte of interest" such as glucose. Berner, 22:18-21 (emphasis added). Described in the "Baseline Background" section, the "electrochemically active interfering species and/or residual analyte" is expected to have an effect on the raw glucose signal much like the "baseline background" current. *See* Berner, 22:5-21. Ex. 1003, ¶ 240.

A POSITA would have understood that such "electrochemically active interfering species" and/or "residual analyte" are "biochemical species" which are not correlated with glucose concentration but nevertheless interfere with glucose measurement and contribute to the signal artifacts in the raw signal. Ex. 1003, ¶ 241.

Thus, Berner teaches, or at least suggests, "wherein the non-glucose rate limiting phenomenon is associated with a biochemical species" and renders claim 25 obvious. Ex. 1003, ¶ 242.

B. Ground 2: Claims 37-39 and 41-43 are obvious under 35 U.S.C. § 103 in light of Berner and Schulman.

The combination of Berner and Schulman renders independent claim 37 and each of its dependent claims 38-39 and 41-43 obvious. Ex. 1003, ¶ 243.

1. Independent Claim 37

Independent claim 37 recites identical limitations as independent claim 16 (which are all disclosed, taught or suggested by Berner as shown above), except

that claim 37 adds "wherein the measured signal response is a time-varying voltage response of the electrochemical glucose sensor" to the step of "measure a signal response …" and also includes additional "user interface" functions. Ex. 1003, ¶ 244.

i. "wherein the measured signal response is a time-varying voltage response of the electrochemical glucose sensor"

As shown above in connection with Element [16.e] and claim 20, Berner teaches measuring the "system voltage" or "iontophoresis voltage" during iontophoretic sampling as the "signal response" and further discloses "wherein the measured signal response is a voltage response of the electrochemical glucose sensor." A POSITA would have understood that either of these voltage responses is "time-varying." Ex. 1003, ¶ 245.

For example, the system voltage is assessed to determine whether a high skin resistance has caused too high a voltage level. *See* Berner, 20:40-46. In other words, the level of the system voltage indicates the amount of skin resistance. As is well known in the art, a patient's skin resistance naturally fluctuates as a result of time-varying conditions such as skin temperature, hydration, electrolyte levels, stress, and the presence of perspiration etc., thereby causing the measured system voltage to change over time. Thus, the measured system voltage (*i.e.*, "signal response") is "a time-varying voltage response of the electrochemical glucose

sensor" as claimed. Ex. 1003, ¶¶ 246-247.

Similarly, Berner teaches monitoring the iontophoresis voltage for "Voltage Stability." *See* Berner, 21:37-44. In particular, "the percentage ***difference*** between ***successive*** cathodal or anodal iontophoresis voltages" is determined, suggesting the cathodal or anodal iontophoresis voltages are changing over time and could be unstable. Thus, the measured iontophoresis voltage (*i.e.*, "signal response") is "a time-varying voltage response of the electrochemical glucose sensor" as claimed. Ex. 1003, ¶¶ 248-249.

Therefore, Berner discloses "wherein the measured signal response is a time-varying voltage response of the electrochemical glucose sensor." Ex. 1003, ¶ 250.

ii. "user interface" limitation

Claim 37 recites "a user interface" configured to:

> display a first screen presenting generated glucose concentration data over a first time period,
>
> display a second screen presenting generated glucose concentration data over a second time period, wherein the second time period is different in length from the first time period,
>
> display a third screen presenting the estimated glucose concentration value,
>
> allow a user to toggle between the first screen, the second screen, and the third screen, and
>
> generate an alert responsive to detection of a hyperglycemic

condition or a hypoglycemic condition.

Berner generally discloses "an optional liquid crystal display (LCD) [that] can provide visual prompts, ***readouts*** and ***visual alarm indications***." Berner, 19:12-15 (emphasis added). In particular, Berner describes the "setting and ***display of high and low analyte value alarms***, … and ***display of stored readings***." *Id*., 19:18-23 (emphasis added). Tamada, which Berner incorporates by reference, describes that the biosensor display "may be used, for example, to allow patients to ***scroll through their present and previous analyte (e.g., glucose) level readings*** and to ***alert patients to fluctuations in their levels***." Tamada, 30:15-18 (emphasis added). Ex. 1003, ¶¶ 252-253.

Based on Berner's and Tamada's description, a POSITA would have understood that scrolling through present and previous glucose readings involves displaying multiple screens as the display of each of the present and previous glucose readings may provide a different screen "presenting generated glucose concentration data" over a corresponding time period or "presenting the estimated glucose concentration value" as claimed. Furthermore, the scrolling requires toggling between the multiple screens to the extent only a single value or one set of data is shown on each screen. A POSITA would also have understood that the "high and low analyte value alarms" in the context of glucose monitoring correspond to alerts of a hyperglycemic condition and a hypoglycemic condition

respectively. Ex. 1003, ¶ 254.

Thus, Berner discloses, teaches, or suggests at least "a user interface configured to" display multiple screens presenting "generated glucose concentration data" or "the estimated glucose concentration value," "allow a user to toggle between" the multiple screens, and "generate an alert responsive to detection of a hyperglycemic condition or a hypoglycemic condition." Ex. 1003, ¶ 255.

The only user interface limitations recited in claim 37 that are not explicitly described by Berner are the "glucose concentration data" being generated over "a first time period" and "a second time period" respectively and those time periods being "different in length." Ex. 1003, ¶ 256.

Schulman (Ex. 1008), which is directed to "[a] glucose monitoring system that continuously measures the glucose concentration in a patient's blood" (Schulman, 2:27-30), discloses all the user interface limitations of claim 37. In particular, Schulman discloses:

> "The glucose monitor 34 displays the ***current glucose concentration*** and the ***trend*** (the rate of change over a previous period of time, e.g., fifteen minutes). The glucose concentration is presented as either a digital display of the current value, or as a graph. The concentration value is updated once each minute (or other prescribed interval). ***In the graphic display mode, the concentration is plotted at user selected***

> ***intervals, showing periods of 3 to 72 hours*** … ***In the monitor mode, the glucose concentration is displayed in large numerals*** that can be easily seen from across the room, as illustrated, e.g, in FIG. 10B."

Schulman, 12:51-64 (emphasis added). *See also* Schulman, FIG. 10B ("Current Value" mode or "monitor mode"), FIG. 10C ("Graph" mode). Ex. 1003, ¶¶ 257-258.

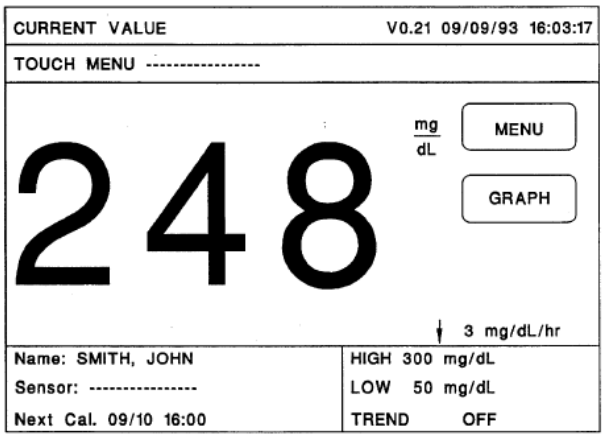

FIG. 10B

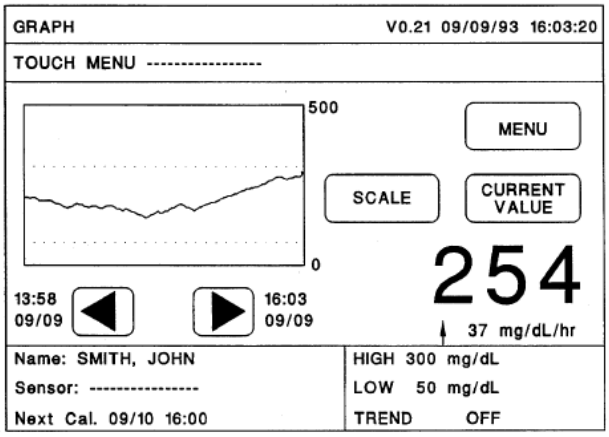

FIG. 10C

A POSITA would have understood that Schulman discloses all three types of user interface "screens" and related toggling as recited in claim 37. Ex. 1003, ¶ 259.

First, in the "graphic display mode," Schulman teaches that a user could select different time periods of 3 to 72 hours to plot glucose concentration data. Schulman, 12:51-64. Thus, if the user chose a 3-hour period for the graphic display, then the glucose monitor would "display a first screen presenting generated glucose concentration data over a first time period [of 3 hours]"; if the

user chose a 72-hour period for the graphic display, then the glucose monitor would "display a second screen presenting generated glucose concentration data over a second time period [of 72 hours], wherein the second time period is different in length from the first time period" as claimed. Ex. 1003, ¶ 260.

Second, in the "monitor mode," Schulman teaches that a different screen displays the glucose concentration "in large numerals." Ex. 1008, 12:62-64. In other words, the monitor mode "display[s] a third screen presenting the estimated glucose concentration value" as claimed. Ex. 1003, ¶ 261.

Third, Schulman discloses that various menu buttons can be selected by the user to switch between the display modes and screens:

> "FIG. 10A, for example, shows the main menu screen displayed by the glucose monitor when in use. ***FIG. 10B depicts the current value screen displayed by the monitor when the current value selection is made from the main menu.*** Note the large size of the glucose measurement displayed, providing easy-to-read numbers that are several inches high. ***FIG. 10C depicts a representative graph of the glucose concentration that is generated and displayed by the glucose monitor when the graphic selection is made from the main menu.***"

Schulman, 14:42-51 (emphasis added). The ability to switch display modes, coupled with the above-described ability to select time periods of different length

to plot data, "allow[s] a user to toggle between the first screen, the second screen, and the third screen." Ex. 1003, ¶ 262.

In addition, much like Berner, Schulman also teaches "generate an alert responsive to detection of a hyperglycemic condition or a hypoglycemic condition." *See* Schulman, 2:29-32 ("The system further automatically determines whether the measured concentration and rate of change are within certain preset limits, and if not, generates an alarm signal."); *id*., 13:17-21 ("an alarm that signals when the value of the most recent reading is below or above user-set (or, if none, default) low or high limits"). Ex. 1003, ¶ 263.

Therefore, Schulman discloses all the "user interface" limitations of claim 37, and the combination of Berner and Schulman teaches or suggests all the elements of claim 37. Ex. 1003, ¶ 264.

iii. A POSITA Would Have Been Motivated To Combine Schulman with Berner.

A POSITA would have been motivated to combine Schulman's disclosure with Berner's glucose sensor to improve its user interface capabilities. Ex. 1003, ¶ 265.

First, Berner and Schulman are in the same field of endeavor, both being directed to continuous glucose monitoring and both disclosing complete glucose sensor systems including user interfaces. In both systems, the continuous

measurement generates a series of glucose concentration data that need to be presented and utilized via a user interface. Ex. 1003, ¶ 266.

Second, the user interfaces disclosed by Berner and Schulman already have substantially overlapping display and alarm functions. For example, Berner discloses "an optional liquid crystal display (LCD) [that] can provide visual prompts, readouts and visual alarm indications" (Berner, 19:12-15); Schulman describes "a large screen 126 wherein the sensor data, including glucose concentration, rates of change, and history (graphs of glucose concentration over time) may be displayed" (Schulman, 11:14-18) as well as alarms to signal when glucose values exceed high or low limits (*id*., 13:17-21). The only significant difference is in Schulman's capability of displaying glucose graphs over different time periods. Ex. 1003, ¶ 267.

Third, Schulman's additional teaching is complementary to Berner because Schulman offers user interface functions suggested by, but not explicitly disclosed in, Berner. Berner, on the one hand, recognizes the need for "a subject to detect blood glucose ***swings or trends*** indicative of hypoglycemic or hyperglycemic episodes." Berner, 34:29-35 (emphasis added). Schulman, on the other hand, acknowledges the advantage of detecting "trends" and accordingly teaches that "[s]uch stored data may also advantageously be viewed, as selected, as a graphic display that indicates the last several hours of recorded values, ***thereby clearly***

showing any <u>trends</u> in the data over such time period." Schulman, 2:57-61 (emphasis added). That is, Schulman teaches displaying glucose graphs over user-selectable time periods to help visualize and detect the trends in glucose measurement. In light of these teachings, a POSITA could readily appreciate that Schulman's graphical display functions directly meet Berner's stated need for detecting and displaying data trends. Thus, Berner itself provides the reason and incentive for adopting Schulman's user interface functions. Ex. 1003, ¶¶ 268-271.

Fourth, a POSITA would have been capable of modifying Berner's biosensor display to incorporate Schulman's graphical display functions. Since Berner already discloses most of the claimed user interface functions, only a small amount of modification would be required, such as reprogramming the microprocessor and reconfiguring the user interface with enhanced graphical display of glucose graphs over user-selectable time periods. At the time of the claimed invention (in 2003), no significant technological obstacle would have prevented a POSITA from making such modification. Ex. 1003, ¶ 272.

After all, the user interface and its functions are substantially independent from the glucose sampling and sensing components and related functions. A POSITA would have considered the user interface in Berner's system to be a modular component that could be easily copied and adapted from a similar continuous glucose sensor system such as Schulman's. Ex. 1003, ¶ 273.

Thus, modifying Berner with Schulman would require little more than: (a) combining one known element in the prior art (*i.e.*, Schulman's display functions) with other known elements (*i.e.*, Berner's biosensor system), or (b) simply substituting one known element (*i.e.*, the user interface of Berner's biosensor system) with another known element (*i.e.*, Schulman's user interface module). Therefore, a POSITA would have a reasonable expectation of success in making the combination or modification. Ex. 1003, ¶¶ 272-273.

To the extent Patent Owner attempts to limit Berner's disclosure to its preferred wristwatch embodiment and cite its screen size constraint, it should be noted that the choice of user interface hardware (*e.g.*, display screen) here is a design choice well within a POSITA's technical capabilities. Ex. 1003, ¶ 274. For example, Schulman teaches coupling its glucose monitor to multiple sensors through "a ***detachable connector*** that does not use a direct electrical contact (i.e., a ***'contactless' connector***)" (Schulman, 5:1-10, 11:28-12:13, FIGs. 7A-7B), which suggests that the user interface of a continuous glucose monitor need not be permanently attached to the sensor components as in Berner's wristwatch embodiment. As a result, a POSITA would have considered choosing a larger, detachable display unit when modifying Berner with Schulman. Ex. 1003, ¶ 275.

In summary, because (1) Berner and Schulman are in exactly the same field, (2) they already disclose substantially overlapping user interface functions, (3)

Berner itself offers the motivation to adopt Schulman's enhanced graphical display function in order to help visualize data trends, and (4) the insignificant amount of modification required would be well within the grasp of a POSITA, it would have been obvious to combine the teachings of Berner and Schulman to make the claimed invention. Ex. 1003, ¶¶ 266-275.

Since it would have been obvious for a POSITA to combine Berner and Schulman which collectively teach or suggest each and every element of claim 37, Berner, in view of Schulman, renders claim 37 obvious. Ex. 1003, ¶ 276.

2. Dependent Claims 38-39 and 41-43

Dependent claims 38-39 and 41-43 each incorporate the limitations of independent claim 37 (which are all taught or suggested by Berner and Schulman) and additionally recited limitations identical to those of dependent claims 17, 21, and 23-25 respectively which are also disclosed, taught, or suggested by Berner. Ex. 1003, ¶ 277. Thus, Berner discloses, teaches, or suggests the additionally recited limitations of claims 38-39 and 41-43.

Therefore, based on the same reasons explained above for combining Berner and Schulman, their combination renders each of claims 38-39 and 41-43 obvious. Ex. 1003, ¶ 278.

VII. CONCLUSION

In light of the above, it is respectfully submitted that claims 16-21, 23-25,

37-39, and 41-43 of the ’045 Patent are unpatentable under 35 U.S.C. § 103. Petitioner respectfully requests that an *inter partes* review be instituted and the subject claims be cancelled.

VIII. MANDATORY NOTICES

A. Real Parties-In-Interest Under 37 C.F.R. § 42.8(b)(1)

Petitioner identifies AgaMatrix, Inc. as the real party-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

As of the filing date of this petition, the ’045 Patent is involved in litigation in the District of Delaware in *Dexcom, Inc. v. AgaMatrix, Inc.*, Case No. 1:17-cv-01310; and subsequently before United States International Trade Commission, in *Certain Electrochemical Glucose Monitoring Systems And Components Thereof*, Investigation No. 337-TA-1075.

Concurrently with this petition, Petitioner is also filing: (a) an IPR petition (IPR2018-01716) to challenge the patentability of substantially the same claims of the ’045 Patent on different, but equally compelling, grounds; and (b) IPR petitions (IPR2018-01717 and IPR2018-01718) to challenge the patentability of certain claims of U.S. Patent No. 9,750,460 which is commonly owned, and shares the same specification and parents, as the ’045 Patent.

Petitioner is not aware of any other judicial or administrative matter that would affect or be affected by a decision in this IPR.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3) and Service Information Under 37. C.F.R. § 42.8(b)(4)

Lead Counsel	*Back-up Counsel*
Ira J. Levy (Reg. No. 35,587) ILevy@goodwinlaw.com GOODWIN PROCTER LLP 620 8th Avenue New York, NY 10018 (212) 813-8800	Ce Li (Reg. No. 70,305) CLi@goodwinlaw.com GOODWIN PROCTER LLP 901 New York Avenue NW Washington, DC 20001 (202) 346-4000

Pursuant to 37 C.F.R. § 42.8(b)(4), counsel agrees to service by mail as detailed above, and to electronic service by email to the email addresses above. A Power of Attorney executed by Petitioner accompanies this Petition.

Fees: The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 506989.

D. Service on the Patent Owner

Pursuant to 37 C.F.R. § 42.105(a), this petition and its exhibits were served simultaneously with this filing on Patent Owner at the correspondence address of record on file at the USPTO for the ’045 Patent, per the attached Certificate of Service, with a copy to Patent Owner’s counsel in the above-referenced litigation matters.

IX. GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.104, Petitioner certifies that this Petition is being filed within one year of AgaMatrix, Inc. being served with a complaint for infringement. Petitioner has not filed a civil action challenging the '045 Patent, it is available for *inter partes* review, and that Petitioner is not barred from requesting *inter partes* review of the '045 Patent.[5]

Date: September 14, 2018

Respectfully submitted,

By */s/ Ira J. Levy*

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Attorneys for Petitioner

[5] The Complaint alleging infringement of the '045 Patent in *Dexcom, Inc. v. AgaMatrix, Inc.*, Case No. 1:17-cv-01310 (D. Del.) was served on Sept. 15, 2017.

CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,724,045** complies with the type-volume limitation of 37 C.F.R. §§42.24(a)(1)(i) and 42.24(b)(1). The Petition contains 13,970 words, excluding the parts of the Petition exempted by 37 C.F.R. §42.24(a)(1), as measured by the word-processing system use to prepare the Petition.

Certificate of Service

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105, I hereby certify that on September 14, 2018, I caused a true and correct copy of the foregoing **PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,724,045** and copies of all supporting materials to be served by Federal Express Next Business Day Delivery on the patent owner at the correspondence address of record for the subject patent as listed on PAIR:

Rose M. Thiessen
KNOBBE, MARTENS, OLSON & BEAR, LLP
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FOURTEENTH FLOOR
IRVINE CA 92614

With an additional copy to:

Kirk R. Ruthenberg
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/Ce Li/
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