

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Abbott Diabetes Care Inc.,
Petitioner,

v.

DexCom, Inc.,
Patent Owner.

Case No. IPR2024-00841
Patent No. 10,709,364

**DECLARATION OF DR. ANTHONY EDWARD CASS IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 10,709,364**

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LIST OF EXHIBITS

Exhibit No.	Description of Exhibit
1001	U.S. Patent No. 10,709,364 (“’364 patent”)
1003	Prosecution File History of U.S. Patent No. 10,709,364
1004	Gross et al., <i>Device and Method of Calibrating and Testing a Sensor for In Vivo Measurement of an Analyte</i> , U.S. Patent No. 6,275,717 (issued Aug. 14, 2001) (“ Gross ”)
1005	Feldman et al., <i>A Method of Calibrating an Analyte-Measurement Device, and Associated Methods, Devices and Systems</i> , U.S. Patent Appln. Pub. No. 2005/0239154 (Oct. 27, 2005) (“ Feldman ”)
1006	Feldman et al., <i>A Continuous Glucose Sensor Based on Wire Enzyme™ Technology—Results from a 3-Day Trial in Patients with Type 1 Diabetes</i> , Diabetes Technology & Therapeutics, Vol. 5, No. 5, pp. 769-779 (2003) (“ Feldman-2003 ”)
1007	Nishida et al., <i>Development of a ferrocene-mediated needle-type glucose sensor covered with newly designed biocompatible membrane, 2-methacryloyloxyethyl phosphorylcholine -co-n-butyl methacrylate</i> , Medical Progress through Technology, Vol. 21, No. 2., pp. 91-103 (May 1995) (“ Nishida ”)
1008	Velho et al., <i>Strategies for calibrating a subcutaneous glucose sensor</i> , Biomed. Biochim. Acta, Vol. 48, No. 11/12, pp. 957-964 (1989) (“ Velho ”)
1009	Ward et al., <i>A new amperometric glucose microsensor: in vitro and short-term in vivo evaluation</i> , Biosensors & Bioelectronics, Vol. 17, pp. 181-189 (2002) (“ Ward ”)
1010	Mastrototaro et al., <i>Glucose Monitor Calibration Methods</i> , U.S. Patent No. 6,424,847 (issued July 23, 2002) (“ Mastrototaro ”)
1011	Say et al., <i>Analyte Monitoring Device and Methods of Use</i> , U.S. Patent No. 6,175,572 (issued Jan. 16, 2001) (“ Say ”)

Exhibit No.	Description of Exhibit
1012	Heller <i>et al.</i> <i>Implanted Electrochemical Glucose Sensors for the Management of Diabetes</i> , Annu. Rev. Biomed. Eng., Vol. 1, pp. 153-175 (1999) (“ Heller ”)
1013	<i>Biosensors in the Body: Continuous in vivo Monitoring</i> , Ch. 1: An Introduction to in vivo Biosensing: Progress and Problems (David M. Fraser) (pp. 1-56), Ch. 2: Electrochemical Sensors for in vivo Glucose Sensing (Milena Koudelka-Hep) (pp. 57-77) (ed. David M. Fraser, John Wiley & Sons Ltd. 1997) (“ Fraser ”)

I. INTRODUCTION

1. I, Professor Anthony Edward George Cass, have been retained as an expert witness by counsel for Abbott Diabetes Care Inc. (“Abbott” or “Petitioner”), who I understand is the Petitioner in the present proceeding. I have been asked to consider whether U.S. Patent No. 6,275,717 to Gross et al. (Exhibit 1004, “Gross”) discloses and/or renders obvious the elements of claims 1-3, 5, 6, and 8-10 of U.S. Patent No. 10,709,364 B2 (“the ’364 patent”). I also have been asked to consider the state of the art at the time of the alleged invention claimed in the ’364 patent. My opinions are set forth in this declaration, which is based on information currently available to me.

2. I have summarized my educational background, professional experience, and publications in Section II, below.

3. I have been informed that DexCom, Inc. (“DexCom” or “Patent Owner”) purports to own the ’364 patent. To the best of my knowledge, I have no financial interest in DexCom or in the ’364 patent, and to the best of my knowledge, I have had no contact with DexCom or with the named inventors of the ’364 patent. To the best of my knowledge, I have no financial interest in Abbott. To the extent any mutual funds or other investments that I own have a financial interest in DexCom, Abbott, or the ’364 patent, I am not aware of, nor do I have control over, any financial interest that would affect or bias my judgment.

4. I am being compensated at my usual consulting rate of £350 per hour for my work on this matter. My compensation is in no way dependent upon my opinions, testimony, the outcome of this proceeding, or the outcome of any other proceeding relating to the '364 patent.

II. MATERIALS REVIEWED

5. In connection with my analysis and in reaching my opinions stated herein, I reviewed the '**364 patent (Exhibit 1001)**, including claims 1-3, 5, 6, and 8-10 of the patent in view of the specification, and I reviewed the prosecution history of the '364 patent (**Exhibit 1003**). I also reviewed the following documents:

- Gross et al., *Device and Method of Calibrating and Testing a Sensor for In Vivo Measurement of an Analyte*, U.S. Patent No. 6,275,717 (issued Aug. 14, 2001) ("**Gross**"), **Exhibit 1004**
- Feldman et al., *A Method of Calibrating an Analyte-Measurement Device, and Associated Methods, Devices and Systems*, U.S. Patent Appln. Pub. No. 2005/0239154 (Oct. 27, 2005) ("**Feldman**"), **Exhibit 1005**
- Feldman et al., *A Continuous Glucose Sensor Based on Wire Enzyme™ Technology—Results from a 3-Day Trial in Patients with Type 1 Diabetes*, *Diabetes Technology & Therapeutics*, Vol. 5, No. 5, pp. 769-779 (2003) ("**Feldman-2003**"), **Exhibit 1006**
- Nishida et al., *Development of a ferrocene-mediated needle-type glucose sensor covered with newly designed biocompatible membrane, 2-methacryloyloxyethyl phosphorylcholine -co-n-butyl methacrylate*, *Medical Progress through Technology*, Vol. 21, No. 2., pp. 91-103 (May 1995) ("**Nishida**"), **Exhibit 1007**

- Velho et al., *Strategies for calibrating a subcutaneous glucose sensor*, Biomed. Biochim. Acta, Vol. 48, No. 11/12, pp. 957-964 (1989) (“**Velho**”), **Exhibit 1008**
- Ward et al., *A new amperometric glucose microsensor: in vitro and short-term in vivo evaluation*, Biosensors & Bioelectronics, Vol. 17, pp. 181-189 (2002) (“**Ward**”), **Exhibit 1009**
- Mastrototaro et al., *Glucose Monitor Calibration Methods*, U.S. Patent No. 6,424,847 (issued July 23, 2002) (“**Mastrototaro**”), **Exhibit 1010**
- Say et al., *Analyte Monitoring Device and Methods of Use*, U.S. Patent No. 6,175,572 (issued Jan. 16, 2001) (“**Say**”), **Exhibit 1011**
- Heller et al., *Implanted Electrochemical Glucose Sensors for the Management of Diabetes*, Annu. Rev. Biomed. Eng., Vol. 1, pp. 153-175 (1999) (“**Heller**”), **Exhibit 1012**
- *Biosensors in the Body: Continuous in vivo Monitoring*, Ch. 1: An Introduction to in vivo Biosensing: Progress and Problems (David M. Fraser) (pp. 1-56), Ch. 2: Electrochemical Sensors for in vivo Glucose Sensing (Milena Koudelka-Hep) (pp. 57-77) (ed. David M. Fraser, John Wiley & Sons Ltd. 1997) (“**Fraser**”), **Exhibit 1013**

III. PROFESSIONAL BACKGROUND AND QUALIFICATIONS

6. I am currently an Emeritus Professor of Analytical Chemistry and a Senior Research Investigator at Imperial College London.

7. I have more than 45 years of experience working in the field of analytical biotechnology, including in the use of molecular engineering and design to produce new reagents for biosensors and bioanalysis, and in microfabrication for device structures. My research is focused on the area of bioanalysis, with a particular focus on proteomics, microarrays and microfluidics, protein engineering, and biosensors, including biosensor design and calibration. I pioneered the use of

synthetic electron transfer mediators for enzyme biosensors and my work in this area led to the development of the first electronic blood glucose measuring system in 1987, commercialised by MediSense Inc. (now part of Abbott Diabetes Care).

8. In 1974, I received my B.A. with First Class Honors in Chemistry from the University of York. In 1978, I completed my D.Phil in Chemistry at the University of Oxford.

9. In 1980, I completed my Post-doctoral research in Electroenzymology at the University of Oxford, Inorganic Chemistry Laboratory. From 1980-1983, I was a British Petroleum Junior Research Fellow at St. Hugh's College at the University of Oxford.

10. In 1983, I became a Lecturer in Applied Enzymology in the Centre for Biotechnology and Department of Biochemistry at Imperial College London. In 1988, I was promoted to Senior Lecturer. In 1994, I was promoted to Reader in Bioanalytical Chemistry. And in 2001, I was promoted to Professor of Chemical Biology. From 2005 to 2010, I served as the Deputy Director and Research Director for Bio-nanotechnology at the Institute of Biomedical Engineering, Imperial College London. From 2010 to 2023, I was a Professor of Chemistry in the Department of Chemistry at Imperial College London. In 2023, I became an Emeritus Professor.

11. I have also served as a Visiting Professor at various institutions, including the Chinese Academy of Sciences and Universiti Teknologi Malaysia. In 2017, I was a Visiting Professor at the University of Rome, La Sapienza, and in 2023 I was a Visiting Professor at the University of Bari, Italy.

12. I am a Fellow of the Royal Society of Chemistry, and a Fellow of the Royal Society of Biology. I am also a member of the Institute of Engineering and Technology (IET), and a member of the American Chemical Society (ACS).

13. I have received a number of awards throughout my career. I received the Royal Society Mullard Medal (co-awardee) in 1994 for my work in translating fundamental studies of enzyme electron transfer to a commercially successful glucose sensor. I received a Chemical Landmark Award (co-awardee) in 2012 from the Royal Society of Chemistry for making a crucial discovery that led to the development of a unique electronic blood glucose sensor. I received the Sir George Stokes Medal of the Royal Society of Chemistry in 2017 for my work in analytical chemistry over an extended period of time.

14. I have founded multiple companies in the area of biosensors and analytical biotechnology. I am the Founder and Director of Bio Nano Consulting Ltd., the first consulting company in Europe spanning both bio- and nanotechnology. I also founded AquAffirm, a company that develops sensors for food and water quality assurance.

15. I have served on the editorial boards for *Nanobioscience* and *IET Proceedings Nanobiotechnology*, which are peer-reviewed academic journals focused on the interface between nanotechnology and biotechnology. I am also the Specialty Chief Editor of the Medical Diagnostics section of *Frontiers in Lab on a Chip Technologies*.

16. Over the course of my research, I have authored or co-authored over 150 peer-reviewed articles. I am also the editor of three books, including BIOSENSORS: A PRACTICAL APPROACH (1st and 2nd Editions) and IMMOBILISED BIOMOLECULES IN ANALYSIS: A PRACTICAL APPROACH.

17. Additional information regarding my education, work experience, and other qualifications may be found in my curriculum vitae, which is attached as Appendix A to this declaration.

IV. APPLICABLE LEGAL STANDARDS

18. I am not an attorney. For the purposes of this declaration, I have been informed about certain aspects of the law that are relevant to forming my opinions. I have applied the following understanding of the law.

A. Anticipation

19. I have been informed that a patent claim may be “anticipated” if each and every element of that claim is disclosed either explicitly or inherently in a single prior art reference; the elements should be arranged in the reference as in

the claim. Petitioner's counsel has informed me that for a claim element to be inherently disclosed, the prior art reference need not expressly disclose the element so long as the element necessarily flows from a disclosure in the reference.

B. Obviousness

20. I have been informed that a patent claim can be considered to have been "obvious" to a person of ordinary skill in the art at the time of the claimed invention. I have been informed that a claim can be considered obvious even if all of the elements of the claim are not found in a single prior art reference, so long as the differences between the subject matter in the prior art and the subject matter in the claim would have been obvious to a person of ordinary skill in the art at the time of the invention.

21. I have been informed that a determination of whether a claim would have been obvious should be based upon several factors, including, among others:

- the level of ordinary skill in the art at the time of the claimed invention;
- the scope and content of the prior art; and
- what differences, if any, existed between the claimed invention and the prior art.

22. I have been informed that a single reference can render a patent claim obvious if any differences between that reference and the claim would have been obvious to a person of ordinary skill in the art. In addition, a combination of two or more references can render a patent claim obvious, if such a combination would have been obvious to a person having ordinary skill in the art.

23. I have been informed that, when determining whether a patent claim would have been obvious, based on either a single reference or multiple references, it is appropriate to consider, among other factors:

- whether the teachings of the prior art references disclose known concepts that could have been combined in familiar ways to yield predictable results;
- whether a person of ordinary skill in the art could have implemented a predictable variation of the prior art teachings, and would have seen the benefit of doing so;
- whether the claimed elements represent one of a limited number of known design choices, and persons skilled in the art would have reasonably expected the claimed elements to work;
- whether a person of ordinary skill would have recognized a reason to combine known elements in the same manner as recited in the patent claim, and would have reasonably expected success in doing so;

- whether there is some teaching or suggestion in the prior art to modify the prior art teachings, and/or to combine those teachings, and thereby arrive at the combination of elements as claimed in the patent with a reasonable expectation of success; and
- whether the innovation claimed applies a known technique that had been used to improve a similar device or method in a similar way.

24. I also have been informed that a person of ordinary skill in the art has ordinary creativity and is not an automaton. I have been informed that, in considering obviousness, it is important not to determine obviousness using the benefit of hindsight derived from the patent being considered.

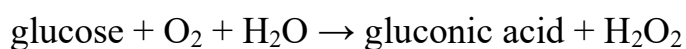
V. TECHNOLOGY BACKGROUND

25. The '364 patent relates generally to continuous glucose monitoring systems and methods. Claims 1-3, 5, 6, and 8-10 of the '364 patent relate to systems and methods for monitoring glucose concentration in subcutaneous tissue, using a transcutaneous electrochemical glucose sensor. Certain elements of the claims relate to sensor sensitivity and calibration. I provide a brief background below on the state of the art in continuous glucose monitors ("CGMs") and their calibration as of March 10, 2005 (the earliest date to which the '364 patent claims priority).

26. Prior to the late 1990s, people with diabetes monitored their blood glucose levels through the use of test strips that required drawing a drop of blood from the finger in a “fingerprick” or “finger-stick.” The test strip containing the blood would be inserted into a device that allowed the patient to read the blood glucose measurement on a screen. The patient would repeat this fingerprick test multiple times a day to monitor his or her blood glucose levels. *See, e.g.,* Fraser at 9 (Ex-1013).

27. Continuous glucose monitors, or CGMs, first became available commercially around the late 1990s as an alternative to the traditional fingerprick tests. These CGMs included an electronic device that adhered to the surface of the patient’s skin, with a transcutaneous electrochemical sensor inserted through the skin and into the interstitial fluid. In these early CGMs, glucose information was collected from the patient and then reviewed by a medical professional.

28. Typically in CGMs (including CGMs on the market today), the transcutaneous electrochemical sensor produces an electrical current that varies depending on the patient’s glucose concentration within the sensor’s range of operation. Many transcutaneous electrochemical sensors use the enzyme glucose oxidase and rely on the following reaction:



For some sensors described in the art, the amount of electrical current that is produced depends on the depletion of oxygen (O_2), while for other sensors, the amount of electrical current produced depends on the generation of hydrogen peroxide (H_2O_2). In either case, the amount of current produced (which is sometimes called the sensor signal or sensor output) should be directly proportional to the concentration of glucose in contact with the sensor. *See, e.g.*, Fraser at 58-59 (Ex-1013); Heller at 157-158 (Ex-1012); Gross (Ex-1004) at 11:11-34.

29. CGMs convert the amount of current generated by the sensor into a glucose level in conventional glucose concentration units (e.g., mg/dL) using a conversion function. The conversion function is sometimes also referred to as a calibration function.

30. The conversion function is determined by a process of sensor calibration. Sensor calibration involves defining a relationship between sensor output (current) and glucose concentration. *See, e.g.*, Fraser at 62-63 (Ex-1013).

31. Typically, as part of sensor calibration, sensor output (in counts or units of current) is matched with a reference or known glucose concentration (in units such as mg/dL). Matched pairs of data points are plotted—for example, with sensor output in counts or units of current as the y-axis value, and a reference glucose concentration as the x-axis value—and a function describing the

relationship of the plotted data points is empirically determined. This empirically-determined function is the conversion function.

32. The conversion function may be a linear or a non-linear function. The conversion function ideally should allow for the calculation of a glucose concentration for any sensor output over the sensor's operating range (such calculation is also sometimes referred to as data calibration) and for the full wear life of the sensor.

33. The conversion function typically defines calibration parameters, such as sensor sensitivity and baseline. Sensor sensitivity is the amount of sensor current generated per unit of glucose concentration in contact with the sensor, and is a measure of the sensor's responsiveness to a concentration of glucose. Baseline (which is sometimes called offset) is the current produced (if any) when no glucose is in contact with the sensor (in other words, it is the background current produced by the sensor).

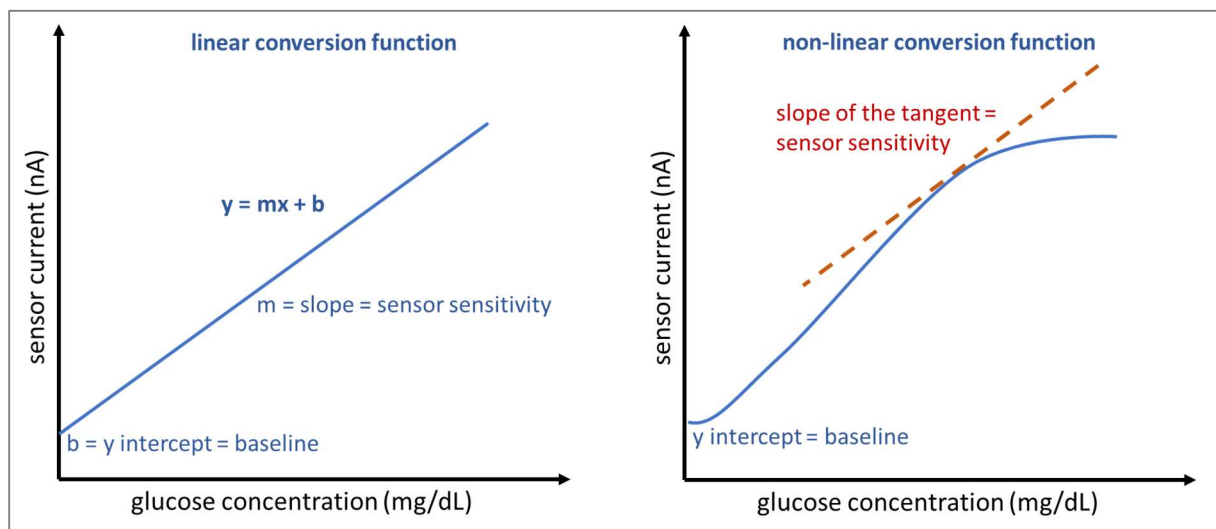
34. When the relationship between glucose concentration x and sensor output y is a linear relationship, the conversion function may be expressed by the equation $y = mx + b$, where:

- y is the sensor signal
- x is the glucose concentration
- m is the sensor's sensitivity to glucose

➤ **b** (which is also the y-intercept) is the baseline signal.

35. The relationship between glucose concentration and sensor output instead may be a non-linear relationship, such as, for example, an exponential or logarithmic relationship. For such relationships, the slope or sensitivity of the sensor may be the first-order derivative of the conversion function—i.e., the slope of the tangent at a given x-axis value; the baseline is the y-intercept of the function.

36. Shown below are two hypothetical plots, where the first plot depicts a linear relationship between sensor output and glucose concentration, and the second plot depicts a non-linear relationship between sensor output and glucose concentration. In the first plot, where the relationship is linear and may be expressed by the equation $y = mx + b$, the slope of the line, m , is sensor sensitivity, and the y-intercept, b , is baseline. In the second plot, where the relationship is non-linear, the slope of the tangent at a given glucose concentration is sensor sensitivity, and the y-intercept of the function describing the relationship is baseline.



37. Accordingly, regardless of whether the empirically-derived conversion function is linear or non-linear, the function—and its corresponding line or curve—is information associated with the sensitivity of the sensor.

38. The conversion function, and therefore sensor sensitivity, can be determined by measuring sensor output in different environments and under different conditions.

39. For example, when sensors are manufactured, sensor output typically is tested at the laboratory or in the manufacturing facility; such an environment is referred to as an in-vitro environment. In the in-vitro setting, sensor output can be measured, for example, in buffer solutions having known glucose concentrations; sensors can be placed in a series of beakers, each beaker containing a solution having a known glucose concentration. For each measurement, the sensor signal and the known glucose concentration would form a “matched pair.” An in-vitro

conversion function can be empirically determined by plotting matched pairs, and the sensitivity defined by the in-vitro conversion function is called in-vitro sensitivity.

40. An in-vivo conversion function can be determined by measuring sensor output with respect to glucose concentration when the sensor has been inserted into a host's subcutaneous tissue—i.e., in an in-vivo environment. Typically, to determine an in-vivo conversion function, one or more reference glucose concentrations is used to generate the “matched pairs”: for example, a fingerprick test can provide a reference (in this case, blood) glucose concentration value, and this value can be matched with the sensor's output measured in the subcutaneous tissue to form a matched pair.¹ Plotting matched pairs allows the determination of the in-vivo conversion function. Such an in-vivo conversion function defines the sensor's in-vivo sensitivity.

¹ When using blood to obtain the reference glucose concentration value, ideally the relationship between blood glucose level and interstitial glucose level (in the subcutaneous tissue) is a linear relationship.

VI. OVERVIEW OF THE '364 PATENT

A. '364 Patent Specification

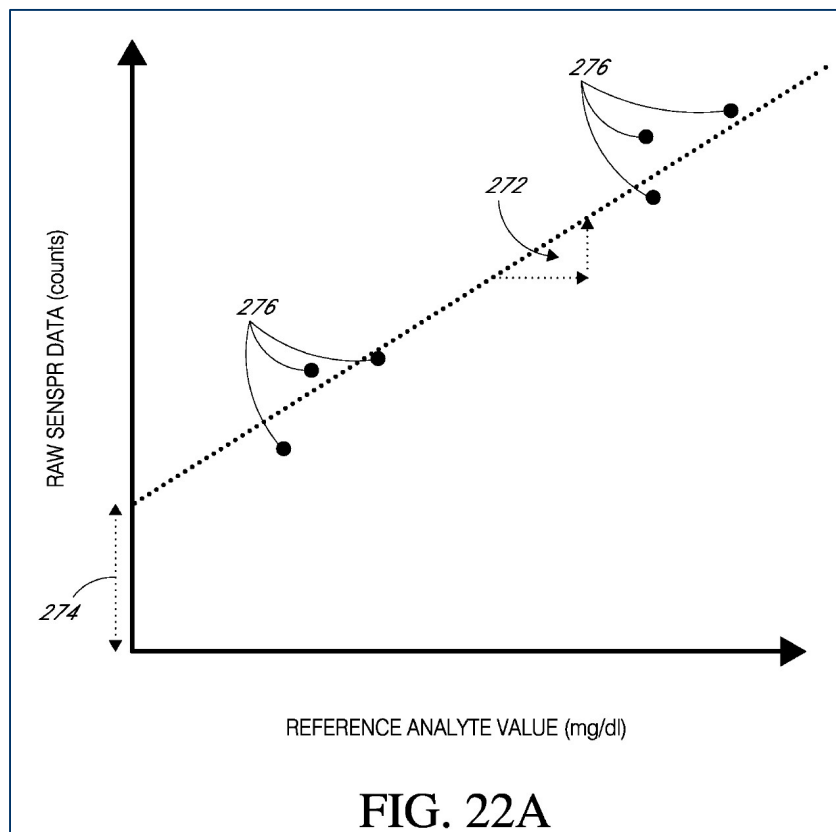
41. The '364 patent relates to “systems and methods for analyte sensor data processing” and particularly “to calibration of sensors.” Ex-1001, 1:29-31. The patent focuses on embodiments for calibrating “long term sensor data using sensor data from another sensor,” such as a “short term” sensor. Ex-1001, 2:4-16; see generally Ex-1001, 1:66-4:45 (Summary of Invention). Such embodiments for performing sensor calibration described in the patent require reference data, obtained via measurements taken by a short-term sensor implanted in the host, to calibrate a long-term sensor (also implanted in the host). E.g., Ex-1001, 2:13–4:45.

42. The '364 patent also describes well-known techniques for calibrating sensor data, such as by using “matched data pairs.” The patent explains that “matched data pairs” refers to “reference data (e.g., one or more reference analyte data points) matched with substantially time corresponding sensor data (e.g., one or more sensor data points).” Ex-1001, 12:18-24; *see also* Ex-1001, Abstract (“The sensor can be calibrated using a calibration set of one or more matched sensor and reference analyte data pairs.”). The patent describes embodiments of using matched data pairs to derive a conversion function (which in the '364 patent embodiments is a linear equation, $y=mx+b$), for converting sensor signal data into glucose concentration values. Ex-1001, 78:24-25, 79:49.

43. FIG. 22A illustrates an embodiment of using matched data pairs to derive a conversion function. As explained in the '364 patent:

FIG. 22A is a graph that illustrates a regression performed on a calibration set to create a conversion function in one exemplary embodiment. In this embodiment, a linear least squares regression is performed on the initial calibration set. The x-axis represents reference analyte data; the y-axis represents sensor data. The graph pictorially illustrates regression of the matched pairs 276 in the calibration set. Regression calculates a slope 272 and an offset 274 ($y = mx + b$), which defines the conversion function.

Ex-1001, 78:17-25. FIG. 22A is reproduced below:



The “reference analyte” values can be blood glucose values. E.g., Ex-1001, 80:37-40 (describing the graph in FIG. 22B, for which the x-axis label is “Reference Glucose Data (mg/dL),” and explaining that the “x-axis represents reference glucose data (blood glucose) from a reference glucose source in mg/dL”).

44. The ’364 patent also describes an embodiment of a conversion function—which in the case of the ’364 patent is a linear equation—at 89:40-47:

As discussed herein, calibration of an enzyme-electrode based glucose sensor consists of solving the line

$$y=mx+b$$

for m and b, where y denotes the sensor signal (in units of A/D counts), x the estimated glucose concentration (mg/dl), m the sensor sensitivity to glucose (counts/mg/dl), and b the baseline signal unrelated to glucose (counts).

B. Priority Date

45. The ’364 patent claims priority to a provisional application filed on March 10, 2005. Ex-1003 at 6, 72, 219. I have been instructed by counsel to apply March 10, 2005 as the priority date and date of the claimed invention for the purposes of my analysis.

C. Claims 1-3, 5, 6, and 8-10

46. Claims 1-3, 5, 6, and 8-10 of the ’364 patent, which I understand are the claims Petitioner is challenging in this proceeding, relate to glucose monitoring systems and to methods for calibrating glucose sensor data, where the systems

store and the methods use information that is “based at least in part on corrections” for a difference between the sensor’s in-vitro sensitivity and in-vivo sensitivity. Claims 1, 5 and 10 are independent claims, and claims 2, 3, 6, 8, 7, and 9 are dependent claims.

47. Independent claim 1 is a system claim that recites the following elements:

- “the transcutaneous electrochemical sensor is characterized by an in vivo sensitivity and an in vitro sensitivity, where the in vivo sensitivity is different from the in vitro sensitivity, and wherein the in vitro sensitivity is predictive of the in vivo sensitivity due to a relationship therebetween;” and
- “a memory,” “wherein the memory has stored therein information associated with the in vivo sensitivity of the transcutaneous electrochemical glucose sensor, wherein the information associated with the in vivo sensitivity is based at least in part on corrections for the difference between the in vivo sensitivity and the in vitro sensitivity of the transcutaneous electrochemical glucose sensor.”

48. Claim 1 does not recite any particular kind of “relationship” between in-vitro and in-vivo sensitivities; nor does claim 1 recite any particular level or

degree by which the in-vitro sensitivity must be “predictive of” the in-vivo sensitivity.

49. In addition, claim 1 does not require any prior knowledge or prior information (information obtained prior to sensor insertion) regarding the relationship between in-vitro sensitivity and in-vivo sensitivity, or regarding how the sensitivities differ from each other. In particular, claim 1 does not require that the stored information be obtained prior to sensor insertion.

50. Independent claims 5 and 10 are method claims. These claims require calibrating sensor data (claim 5) or generating calibrated sensor data (claim 10), using “information associated with an in vivo sensitivity” of the sensor, wherein such information “is based at least in part on corrections for a difference between the in vivo sensitivity and an in vitro sensitivity” for the sensor. Claims 5 and 10 do not recite the “predictive” relationship element of claim 1.

51. Regarding the “corrections for a difference” element, claims 5 and 10, like claim 1, do not require any prior information (information obtained prior to sensor insertion) regarding a difference in sensitivities. Thus none of the independent claims requires any prior information or prior knowledge regarding sensor sensitivity. In particular, the independent claims do not require that any information about sensitivity differences, or about the in-vitro/in-vivo sensitivity relationship, be known or obtained prior to sensor insertion.

52. The remaining challenged claims—claims 2, 3, 6, 8, 7, and 9—are dependent claims. Dependent claim 2 requires that the relationship between the in-vivo sensitivity and in-vitro sensitivity referenced in claim 1 be “established empirically by performing a clinical study.” Dependent claim 3 requires that the in-vivo sensitivity is greater than the in-vitro sensitivity. Dependent claim 6 requires “no user calibrations after” sensor insertion into the host. And dependent claims 8 and 9 relate to the in-vitro sensitivity of the sensor.

D. Prosecution History

53. The '364 patent was filed as U.S. Patent Application No. 16/690,977 on November 21, 2019. Ex-1003 at 219. The patent claims priority to a provisional application filed on March 10, 2005. For this declaration, I have been asked to assume that the priority date of the '364 patent is March 10, 2005.

54. The application for the '364 patent was filed with 20 claims, along with a “Track One” request for prioritized examination. Ex-1003 at 1, 69-71.

55. On December 16, 2019, the applicant filed an information disclosure statement (“IDS”) that listed a number of documents and spanned 273 pages. Ex-1003 at 225-501.

56. On January 2, 2020, the applicant canceled claims 1-20 and added claims 21 and 22, which are shown below (*see* Ex-1003 at 502-506):

AMENDMENTS TO THE CLAIMS

- 1-20. (Canceled)
21. (New) A glucose monitoring system comprising:
a transcutaneous glucose sensor having an in vivo portion and an ex vivo portion.
22. (New) A method for calibrating data from a transcutaneous glucose sensor, the method comprising:
receiving sensor data from the transcutaneous glucose sensor after the transcutaneous glucose sensor is implanted in a host, wherein the sensor data is indicative of a glucose concentration in the host; and
calibrating, using a processor, the sensor data received from the transcutaneous glucose sensor.

57. In a Non-Final Office Action dated January 22, 2020, the Examiner rejected claims 21 and 22 for being anticipated by the prior art. Ex-1003 at 510-516. The Examiner also electronically initialed the pages of the IDS. Ex-1003 at 520-792.

58. On March 9, 2020, the applicant filed a Response that did not argue that unamended claims 21 and 22 were patentable. Instead, the applicant amended claims 21 and 22 (which issued as claims 1 and 2), and added eight new claims (which issued as claims 3-10). Ex-1003 at 794-801. The amendments to claim 21 are shown below:

AMENDMENTS TO THE CLAIMS

1-20. (Canceled)

21. **(Currently Amended)** A glucose monitoring system comprising:

a transcutaneous electrochemical glucose sensor ~~having~~ comprising an *in vivo* ~~in-vivo~~ portion and an *ex vivo* ~~ex-vivo~~ portion, wherein the transcutaneous electrochemical sensor is characterized by an *in vivo* sensitivity and an *in vitro* sensitivity, wherein the *in vivo* sensitivity is different from the *in vitro* sensitivity, and wherein the *in vitro* sensitivity is predictive of the *in vivo* sensitivity due to a relationship therebetween;

sensor electronics configured to be operably connected to the transcutaneous electrochemical glucose sensor;

a processor configured to be operably connected to the sensor electronics;

a memory configured to be operably connected to the processor, wherein the memory has stored therein information associated with the *in vivo* sensitivity of the transcutaneous electrochemical glucose sensor, wherein the information associated with the *in vivo* sensitivity is based at least in part on corrections for the difference between the *in vivo* sensitivity and the *in vitro* sensitivity of the transcutaneous electrochemical glucose sensor.

59. A Notice of Allowance was mailed on March 25, 2020. Ex-1003 at 805. The '364 patent issued on July 14, 2020. Ex-1003 at 858; Ex-1001.

VII. LEVEL OF ORDINARY SKILL IN THE ART

60. I have been informed that a patent, as well as the prior art, should be interpreted from the perspective of a person of ordinary skill in the art, or POSA, as of the priority date or date of the invention. As noted above, I have been asked to assume that March 10, 2005 is the priority date for purposes of this declaration.

61. A POSA as of the claimed priority date would have had a bachelor's degree in biomedical engineering, chemical engineering, chemistry, or a related or equivalent field, and two or more years of experience researching, developing, designing and/or evaluating (or supervising the same) medical devices for measuring analyte levels, including some experience with algorithms for calibrating such devices, or equivalent experience. Such experience could include either formal coursework in signal processing, computer science, or electrical engineering, or it could also be obtained during on-the-job experience. A person with less or different education but more relevant practical experience, or vice versa, may also meet this standard. A POSA may have been part of an interdisciplinary team with others having the relevant experience set forth above and/or with clinicians. The prior art also evidences the level of skill in the art.

62. Although I am an expert in the field of glucose monitoring systems, I have worked with many persons of ordinary skill over the course of my 45 years of research in this field. My opinions are based on the perspective of the person of ordinary skill in the art.

VIII. CLAIM CONSTRUCTION

63. I understand that in this proceeding, the claims should be construed in accordance with their ordinary and customary meaning in light of the specification, as understood by a POSA.

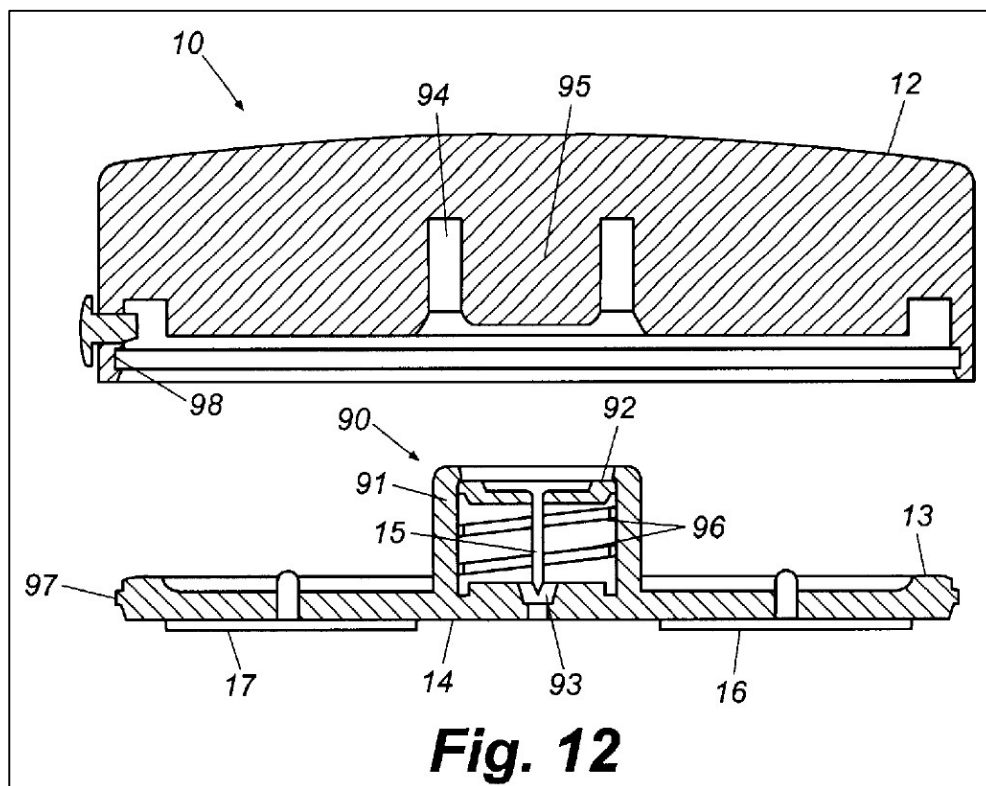
64. For the purpose of this declaration, I have been asked to assume that each claim term is to be given its plain and ordinary meaning, as would be understood by the POSA in the context of the specification, and I have therefore applied the plain and ordinary meaning of each claim term in my analysis. With respect to the scope of claims 2, 8, and 9, I have been asked to apply DexCom's interpretation of the scope of those claims, as discussed further below.

IX. OVERVIEW OF GROSS (EX-1004)

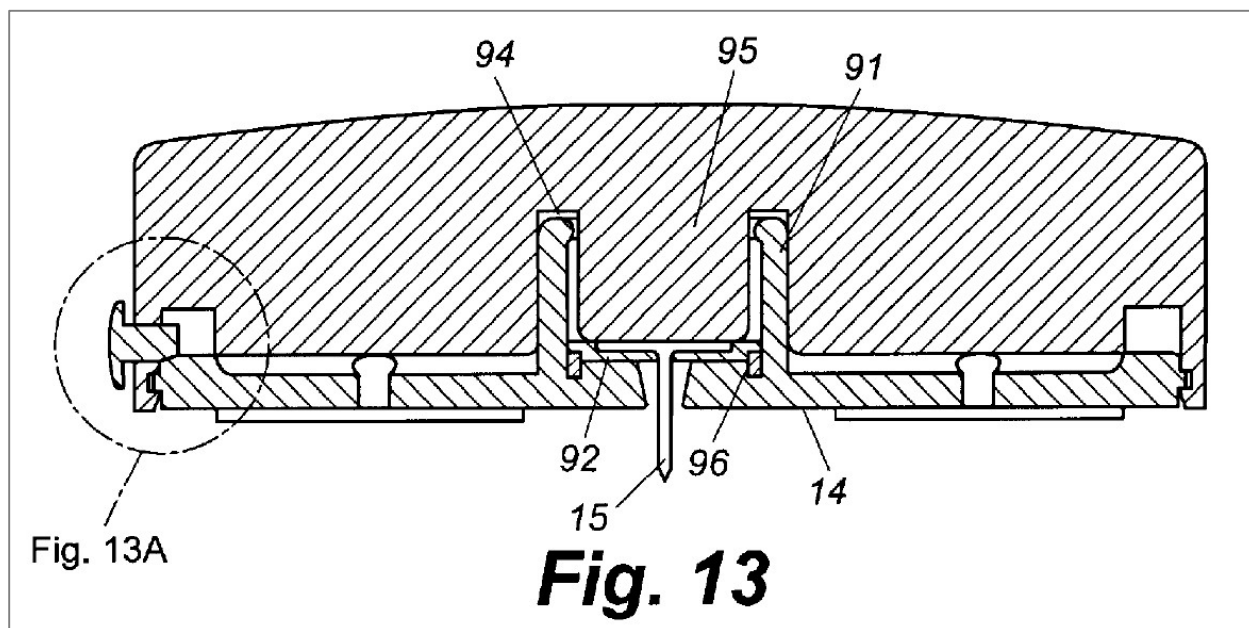
65. U.S. Patent No. 6,275,717, entitled *Device and Method of Calibrating and Testing a Sensor for In vivo Measurement of an Analyte*, issued on August 14, 2001, to Gross et al. and is referred to herein as "Gross." During prosecution of the '364 patent, the applicant listed Gross in an IDS (Ex-1003 at 271), but the Examiner never cited Gross in any rejection.

A. Transcutaneous electrochemical glucose monitoring device

66. Gross describes analyte sensors and methods for calibrating the sensors. Ex-1004, 2:33-8:55, 10:60-14:61. More specifically, Gross describes a two-part monitor device 10: a first part 12 with electronic controlling circuitry and a second part 13 that includes a transcutaneous electrochemical sensor needle 15. Ex-1004, 18:29-45, FIG. 12; *see also* Ex-1004, 10:62-11:4, FIG. 1A. FIG. 12 is reproduced below:



67. In FIG. 13 copied below, Gross illustrates the sensor needle 15 extending through the lower surface 14 of the second part 13 of the device. Gross teaches that the lower surface of the device is to be applied to the user's skin, such that, when applied to the skin, a portion of the sensor penetrates the skin and is in vivo, beneath the user's skin, and a portion of the sensor remains ex vivo, outside of the user's skin. Ex-1004, 5:11-21, 18:35-45, FIG. 13.



68. The monitor device includes a microprocessor, memory, and a display unit for displaying calibrated glucose levels. Ex-1004, 6:62-64, 9:64-65, 10:10-16, 14:30-35.

B. Calibration

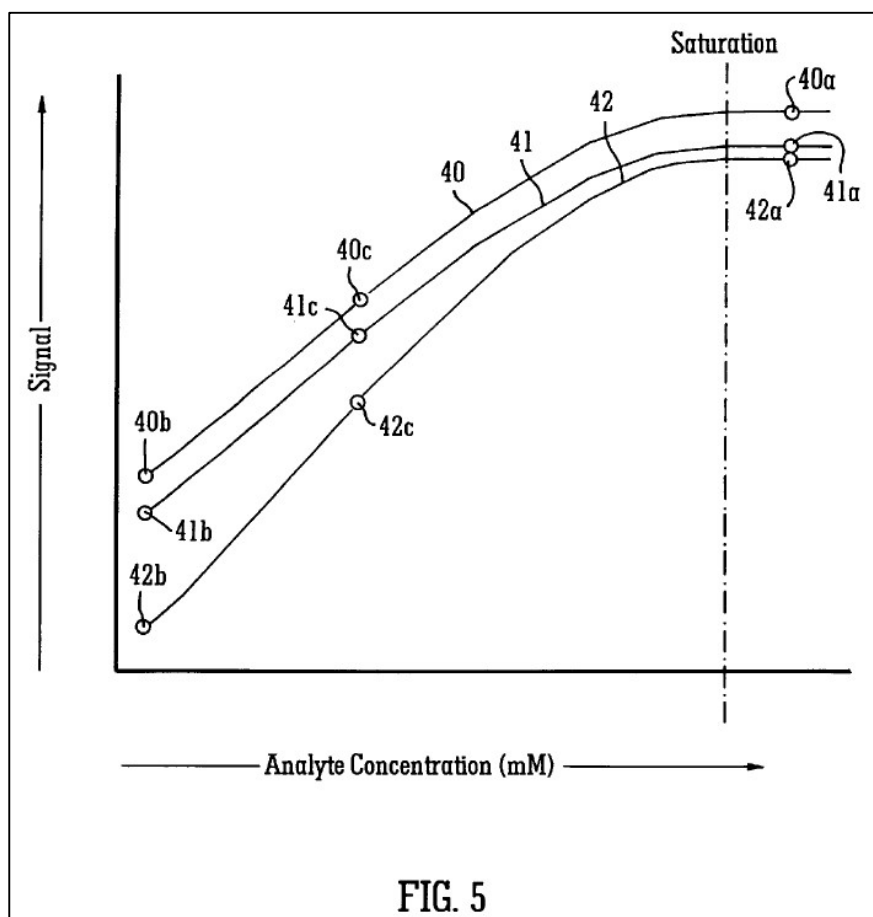
69. Gross teaches methods of calibration that “tak[e] into account the condition of the sensor and the conditions encountered in use.” Ex-1004, 2:55-56. Gross discloses that the curves representing the relationship between sensor output and glucose concentration (and thus the underlying mathematical functions defining these curves) vary in different environments, such as an in-vitro environment and an in-vivo environment. Ex-1004, 9:9-14, 13:42-53, 15:1-13, FIG. 5, FIG.6; *see also* Ex-1004, 1:41-50, 12:45-54.

70. Using Gross's terminology, a curve representing the relationship between sensor output and glucose concentration in an in-vitro environment is referred to as a "theoretical sensor performance curve." Ex-1004, 4:9. A "theoretical sensor performance curve can be determined during the design of the sensor, can be measured for individual sensors during production, or can be measured for a manufactured batch of sensors on a statistical basis." Ex-1004, 4:9-12. In one embodiment, "the theoretical or laboratory-calibrated performance curve [is] measured in the manufacturing facility for the batch of sensor needles[,] ... from tests carried out on a statistically valid sample." Ex-1004, 13:46-53; *see also* Ex-1004, 2:48-51 (explaining that "the theoretical response of the sensor ... can be determined beforehand," i.e., before use of the sensor in a host), 14:5-9 (referring to the "theoretical" curve also as the "laboratory-measured signal-concentration curve"), 14:22-23 (referring to the "theoretical (laboratory measured) curve 40").

71. Gross refers to a curve representing the relationship between sensor output and glucose concentration in an in-vivo environment as a "measured performance curve." Ex-1004, 3:65-67; *see also* Ex-1004, 8:31-44. As explained further below, Gross teaches "extrapolating" this measured performance curve from: (i) two sensor signals measured in vivo and (ii) the knowledge that the theoretical (in-vitro) and measured (in-vivo) curves, while different from each other, share "basic common parameters," i.e., a "common shape" and "similarity in

basic shape.” Ex-1004, 3:40-44, 4:12-16, 14:48-49, 15:1-13. Gross utilizes this observation of the similarity in curve shape between the theoretical (in-vitro) curve and the measured (in-vivo) curve in improved methods of calibration.

72. The steps of Gross’s calibration process are described in detail below, with reference to FIG. 5. FIG. 5 is a graph with analyte (e.g., glucose) concentration on the x-axis, and sensor signal on the y-axis. Three curves are shown in FIG. 5: curve 40, curve 41, and curve 42. As explained in more detail below, curve 40 is a “theoretical” sensor performance curve and shows the relationship between sensor output and glucose concentration in vitro. Ex-1004, 46-50. And each of curve 41 and curve 42 is a “measured performance curve,” showing the relationship between sensor output and glucose concentration in vivo for an individual sensor. Ex-1004, 51-53. FIG. 5 is copied below:



73. A comparison of curves 40, 41, and 42 in FIG. 5 shows that the calibration parameters (sensor sensitivity and baseline) are not the same for the three curves. For example, in-vivo curve 41 is offset on the y-axis when compared to in-vitro curve 40, reflecting that the baseline in the in-vivo environment is different than the in-vitro baseline for a first sensor. In-vivo curve 42 is also offset on the y-axis when compared to in-vitro curve 40. In addition, the slope of curve 42 is steeper than the slope of curve 40, at least at lower concentrations of glucose. These differences in offset and slope show that the baseline and sensitivity in the

in-vivo environment are different from the baseline and sensitivity in the in-vitro environment for the tested sensor.

74. Gross teaches a method as follows: first, a theoretical sensor performance curve “can be determined during the design of the sensor, can be measured for individual sensors during production, or can be measured for a manufactured batch of sensors on a statistical basis.” Ex-1004, 4:9-12; *see also* Ex-1004, 12:30-35 (“The batch of sensor needles ... will have been calibrated in the factory. This is most usually achieved by taking a statistically representative sample of needles from a production batch, carrying out a laboratory calibration (using a standard glucose solution, for example)”). Such in-vitro calibration information of a sensor batch “can be encoded on” the monitor device. Ex-1004, 12:37-38. An example of a theoretical sensor performance curve over the operating range of a sensor is curve 40 in FIG. 5; curve 40 is the “theoretical or laboratory-calibrated performance curve measured in the manufacturing facility for the batch of sensor needles. This curve is the mean calibration curve for the batch of needles, measured from tests carried out on a statistically valid sample.” Ex-1004, 13:46-50.

75. Second, a measured performance curve (a curve representing the relationship between sensor output and glucose concentration in an in-vivo environment) can be extrapolated based the knowledge that in-vitro and in-vivo

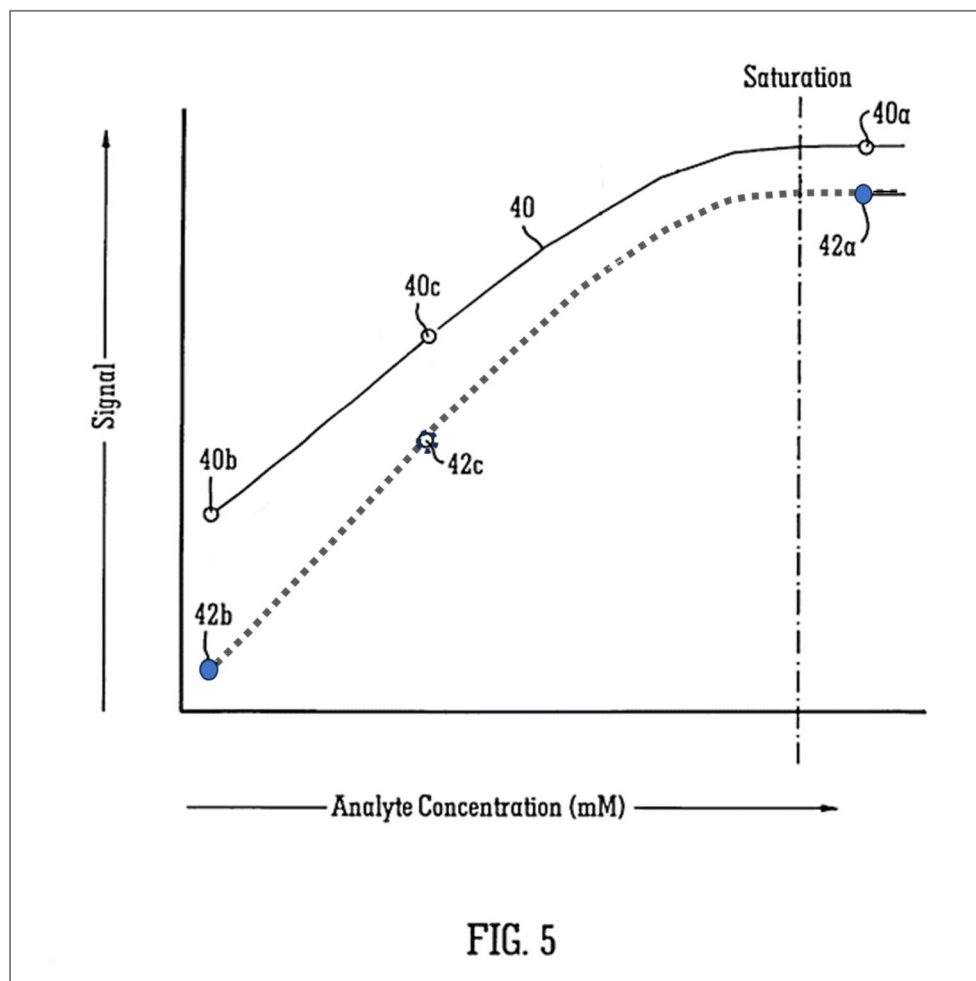
curves have the same basic shape and by measuring the endpoints of the in-vivo curve. In FIG. 5, “[c]urve 41 is the measured performance curve of a first sensor needle in vivo and curve 42 is the measured performance curve of a second sensor needle in vivo.” Ex-1004, 13:51-53.

76. The steps of generating a measured performance curve (e.g., curve 41 or curve 42 in FIG. 5) include measuring the endpoints of the curve. When Gross’s sensor is inserted in a patient, the microprocessor is used to detect up to two sensor signals from the device: a saturation signal and, in some embodiments, a baseline signal. Ex-1004, 3:17-44, 4:17-24, 12:55-13:41, 14:54-61. The saturation signal is a “maximum measurable signal,” and the baseline signal corresponds to background current when substantially no glucose is near the sensor. Ex-1004, 2:57-3:18, 8:25-27, 12:55-13:41. The saturation signal is measured after a coating of glucose on the sensor rapidly dissolves upon implantation and puts the sensor into a saturation regime, a level where the sensor signal has reached its maximum, becoming insensitive to further increases in glucose concentration. Ex-1004, 12:55-13:10. The baseline signal (if desired) is measured after applying a prolonged pulse to consume all the charge carriers near the sensor needle, thereby effectively eliminating the effect of glucose on the sensor output. Ex-1004, 13:19-26. The saturation signal and the baseline signal constitute the “endpoints” of the sensor’s range of operation; for curve 42 in FIG. 5, the saturation signal endpoint

and baseline signal endpoint are points 42a and 42b, respectively. Ex-1004, 3:42, FIG. 5.

77. Gross teaches that, because in-vitro curve 40 and in-vivo curve 42 have a similar shape, measuring the two endpoints 42a and 42b for curve 42 allows the points of the curve between these endpoints to be calculated: “two endpoints may enable the intervening points to be calculated with accuracy.” Ex-1004, 4:19-21; *see also* Ex-1004, 14:48-53 (explaining that “the similarity in basic shape between all three curves 40,41,42” makes it “possible to deduce the mapping of the entire curve [e.g., curve 42] from a small number of measurements”).

78. Annotated FIG. 5 below shows which points on curve 42 are the measured saturation signal and baseline signal endpoints (solid blue points 42a and 42b on curve 42), and shows with a dotted line that the intervening points of curve 42 (including point 42c) have been extrapolated based on the measured endpoints and on the knowledge that curve 42 has the same basic shape as the theoretical sensor performance curve, curve 40 (curve 41 from Gross’s FIG. 5 has been removed in the annotated figure below):



79. Gross further teaches that, as a result of comparing endpoints 42a to 40a, and endpoints 42b to 40b, a calibration function that maps intermediate points from curve 42 onto curve 40 is derived. Ex-1004, 14:10-53. The calculated calibration function “provides complete information for the microprocessor to provide a calibrated output for any subsequent measured signal which lies on” curve 42 during operation. Ex-1004, 14:24-27. *See also* Ex-1004, 14:32-35 (The microprocessor “provides, as an output which is transmitted to the display unit, the calibrated measurement ... which can then be displayed in meaningful units.”),

14:36-38 (“The same basic principles apply to the calibration of the individual sensor needle which has the characteristic measured curve 42.”).

80. Specifically, when calibrating sensor output from a sensor having “characteristic measured curve 42,” the derived or calculated calibration function

must take into account the fact that the difference between the saturation signals 40a, 42a is considerably less than the difference between the base line signals 40b, 42b. Thus, in order to map a measured point 42c onto the corresponding point 40c on theoretical curve 40, the microprocessor must apply a concentration-dependent calibration function in which the amount added to (or subtracted from) the measured signal 42c, when mapping this signal to point 40c, varies in accordance with the position of this point along curve 42c. Nevertheless, it will be appreciated that the similarity in basic shape between all three curves 40,41,42 makes the mapping of any measured curve to the theoretical curve a relatively simple operation, in which it is possible to deduce the mapping of the entire curve from a small number of measurements.

Ex-1004, 14:38-53.

81. Gross also explains the calibration process in its Summary:

[T]he calibration function correlates the measured performance curve with a theoretical sensor performance curve for which there is stored a calibrated output, such that any further sensor signal measurement from the sensor can be calibrated by

correlating the point on the measured performance curve to which the measurement relates with a corresponding point on the theoretical sensor performance curve, and hence with the corresponding calibrated output.

Ex-1004, 8:31-41.

X. GROSS ANTICIPATES AND/OR RENDERS OBVIOUS CLAIMS 1-3, 5, 6, AND 8-10 OF THE '364 PATENT

82. Claims 1-3, 5, 6, and 8-10 of the '364 patent are anticipated by Gross, and/or are rendered obvious by Gross in view of the knowledge of the POSA. An overview of Gross is provided above. My specific analyses of Gross in view of every element of claims 1-3, 5, 6, and 8-10 is provided below.

A. Independent Claim 1

1. 1[Pre]. "A glucose monitoring system comprising:"

83. To the extent the preamble is limiting, Gross discloses it. Gross discloses an "analyte monitor device for the in vivo measurement of an analyte," where "a particularly preferred analyte is glucose." Ex-1004, 4:24-25, 6:28-67, 9:45-47.

2. 1[a]. "a transcutaneous electrochemical glucose sensor comprising an in vivo portion and an ex vivo portion,"

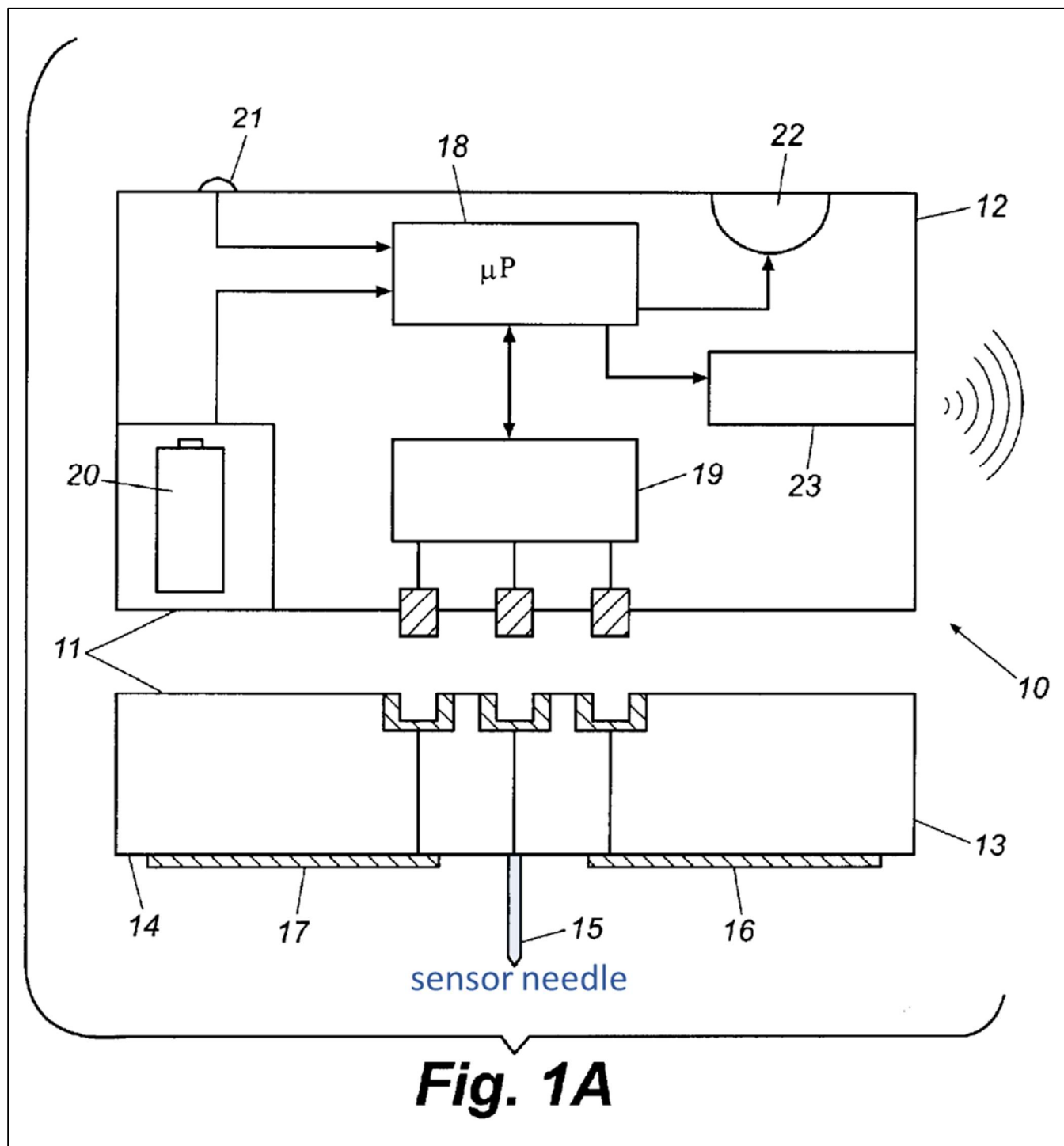
84. Gross discloses the element recited in claim 1[a].

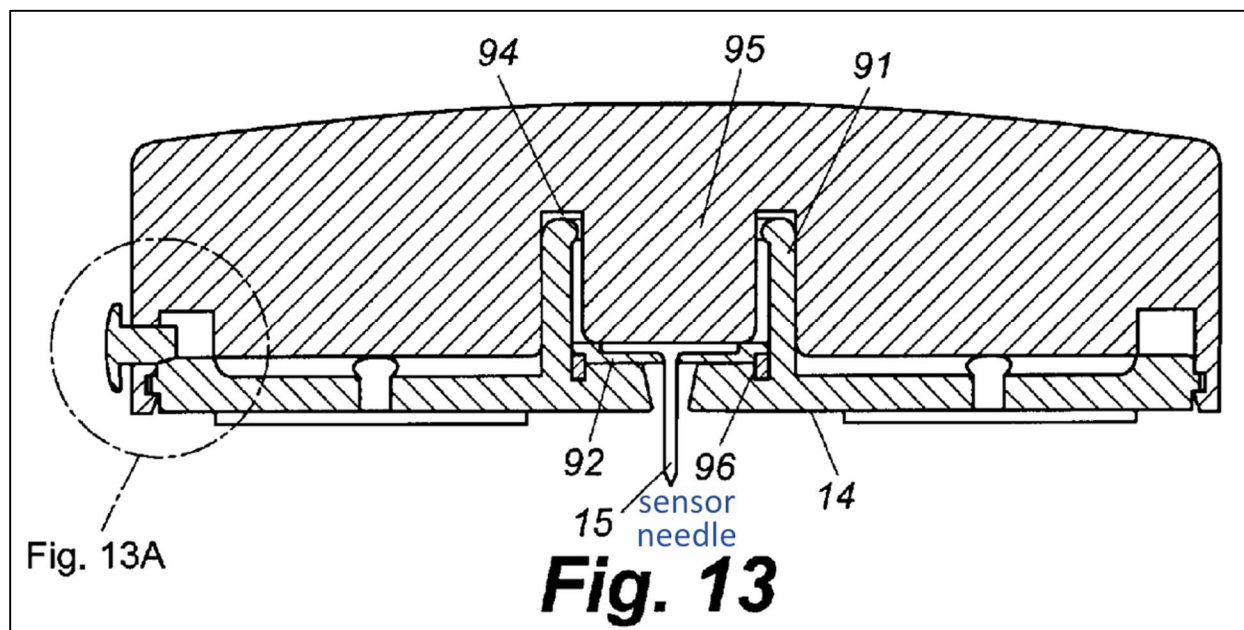
85. Gross's monitor device includes a sensor that comprises an in-vivo portion and an ex-vivo portion. The device includes sensor needle 15, which

“penetrates the skin to a predetermined depth” to contact subcutaneous tissue. Ex-1004, 5:7-21, 10:61-11:4. The sensor remains connected to other portions of the device, such as the reusable first part 12, that remain above the skin. Gross also teaches an embodiment in which the sensor needle extends through an aperture in the lower surface 14 of second part 13 and into the skin of the subject. Ex-1004, 18:35-45, FIG.13.

86. Gross’s sensor needle therefore is a transcutaneous sensor comprising an in-vivo portion (the portion inserted through the skin into the subcutaneous tissue) and an ex-vivo portion (the portion outside the skin that extends into the second part). Indeed, the portion of Gross’s sensor needle 15 that extends into the skin is an “in vivo portion” as defined by the ’364 patent at 11:58-64, and the portion of Gross’s sensor needle 15 that remains outside the body and connected to the other parts of the device is an “ex vivo portion” as defined by the ’364 patent at 11:46-52. *See also* Ex-1001, 27:46-52 (describing the “in vivo portion” and “ex vivo portion” of the sensor).

87. Gross’s FIGS. 1A and 13 are reproduced below; each figure has been annotated to highlight sensor needle 15.





88. Gross's sensor is also an electrochemical glucose sensor. The needle is a platinum-iridium needle containing glucose oxidase. Ex-1004, 10:25-61, 11:11-34. In operation, glucose reacts with oxygen and water to generate hydrogen peroxide. Ex-1004, 11:11-23, 11:60-64. The hydrogen peroxide "serves as a source of electrons which are free to act as charge carriers if a potential is applied between the working electrode (sensor needle) 15 and the counter electrode 16." Ex-1004, 11:31-34. The hydrogen peroxide "is broken down by the platinum in the sensor needle which forms an electrode of an electrical circuit. The level of concentration of glucose is proportional to the magnitude of the current." Ex-1004, 1:21-24; *see also* Ex-1004, 11:24-34. Gross's electrochemical sensor thus operates in the same way as described in the '364 patent for "an enzymatic electrochemical sensor for detecting glucose." Ex-1001, 29:13-24.

3. 1[b]. “wherein the transcutaneous electrochemical sensor is characterized by an in vivo sensitivity and an in vitro sensitivity, wherein the in vivo sensitivity is different from the in vitro sensitivity”

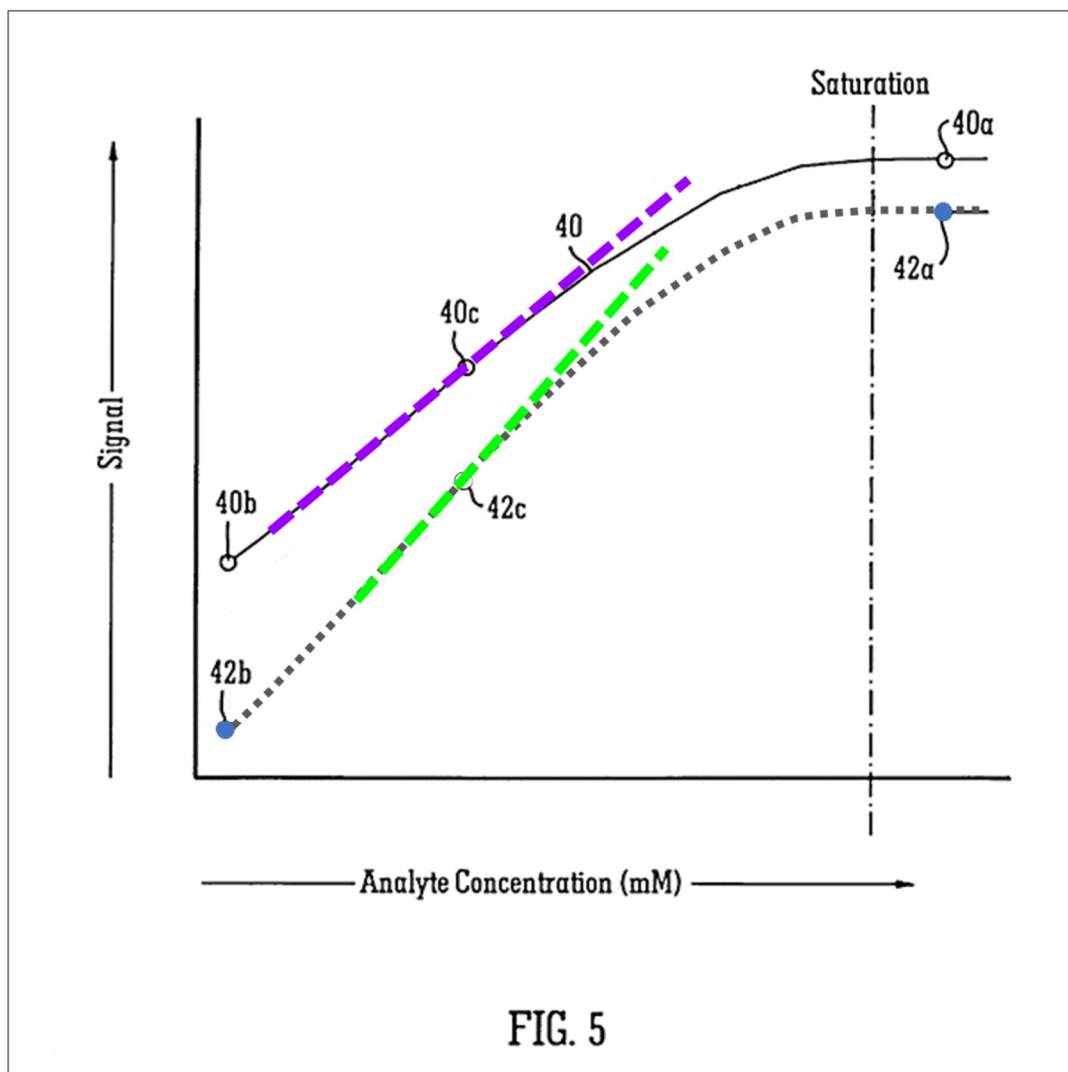
89. Gross discloses the element of claim 1[b]. Gross describes a transcutaneous electrochemical glucose sensor that is characterized by an in-vivo sensitivity and by an in-vitro sensitivity that differ from each other.

90. Gross’s FIG. 5 depicts a “theoretical” (in-vitro) sensor performance curve 40 and a “measured” (in-vivo) performance curve 42 of a sensor. As discussed above, in a plot with analyte concentration on the x-axis and sensor signal on the y-axis (as in Gross’s FIG. 5), sensor sensitivity corresponds to the slope of the curve (e.g., the slope of the tangent on a point on the curve). As shown in annotated FIG. 5 below, the tangent of an intermediate point on curve 42 has a greater (steeper) slope than the tangent of the corresponding intermediate point on curve 40.

91. The tangent of an intermediate point on in-vivo curve 42 (point 42c) is shown by the green dashed line, and the tangent of the corresponding intermediate point on in-vitro curve 40 (point 40c) is shown by the purple dashed line. The slopes of the dashed lines (which are the tangents for intermediate points 40c and 42c) differ from each other—if the tangents had the same slope, they would be parallel to each other and would not intersect at any point; but as can be seen

below, extending each tangent out would result in the two tangents intersecting each other.

92. The different slopes of the tangents of curves 40 and 42 are a consequence of that fact that the difference between signals 40a and 42a is “considerably less” than the difference between signals 40b and 42b. Ex-1004, 14:39-41. The different slopes of these tangents means that the in-vitro sensitivity at this intermediate point (i.e., at the particular glucose concentration on the x-axis for points 40c and 42c) differs from the in-vivo sensitivity.



93. Accordingly, Gross discloses a sensor characterized by an in-vivo sensitivity and an in-vitro sensitivity, wherein the in-vivo sensitivity is different from the in-vitro sensitivity.

4. **1[c]. “and wherein the in vitro sensitivity is predictive of the in vivo sensitivity due to a relationship therebetween;”**

94. Gross discloses the element of claim 1[c].

95. Claim element 1[c] requires that the in-vitro sensitivity is “predictive” of the in-vivo sensitivity “due to a relationship therebetween,” such that the in-

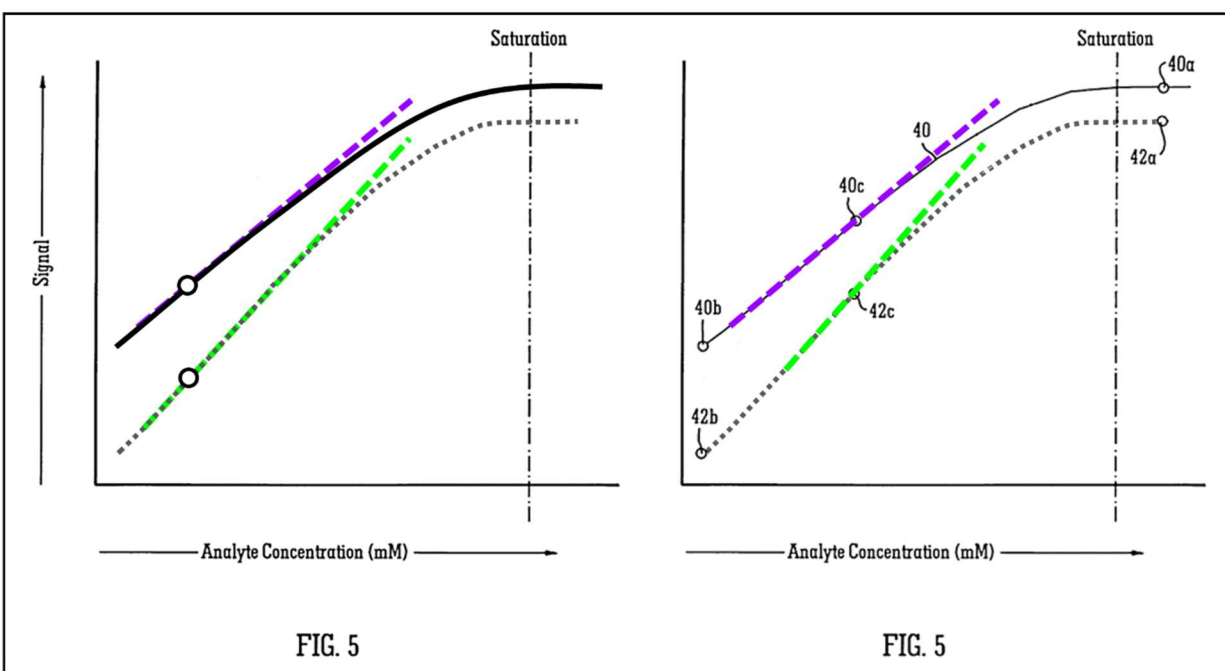
vitro sensitivity could be used to estimate the in-vivo sensitivity. As I noted above, claim 1[c] does not require any particular kind of “relationship” between in-vitro and in-vivo sensitivities; nor does it require any particular level or degree by which the in-vitro sensitivity must be “predictive of” the in-vivo sensitivity. The specification also imposes no such limits; rather, the specification makes clear that a “predictive relationship” includes relationships where in-vitro sensitivity approximates in-vivo sensitivity (although the sensitivities cannot be equal, given claim element 1[b]). Ex-1001, 79:56-63; *see also* Ex-1001, 18:5-9. In particular, the '364 patent provides, as an example, the generic function “ $m \approx f(m_{\text{in vitro}})$ ” to describe “a predictive relationship” between sensitivities. Ex-1001, 79:56-63. In this example, any kind of function “f” is suitable for approximating (“ $\approx$ ”) in-vivo sensitivity from in-vitro sensitivity.

96. Gross teaches that, for the sensor having measured performance curve 42, the in-vitro sensitivity is predictive of the sensor’s in-vivo sensitivity due to a relationship between these sensitivities.

97. Specifically, Gross teaches that a sensor’s measured (in-vivo) performance curve 42 has a similarity in basic shape to theoretical (in-vitro) performance curve 40. Ex-1004, 14:48-53. This similarity in basic shape allows for the estimation or prediction of intermediate points on curve 42, after the baseline and saturation endpoints are measured. Gross teaches extrapolating the

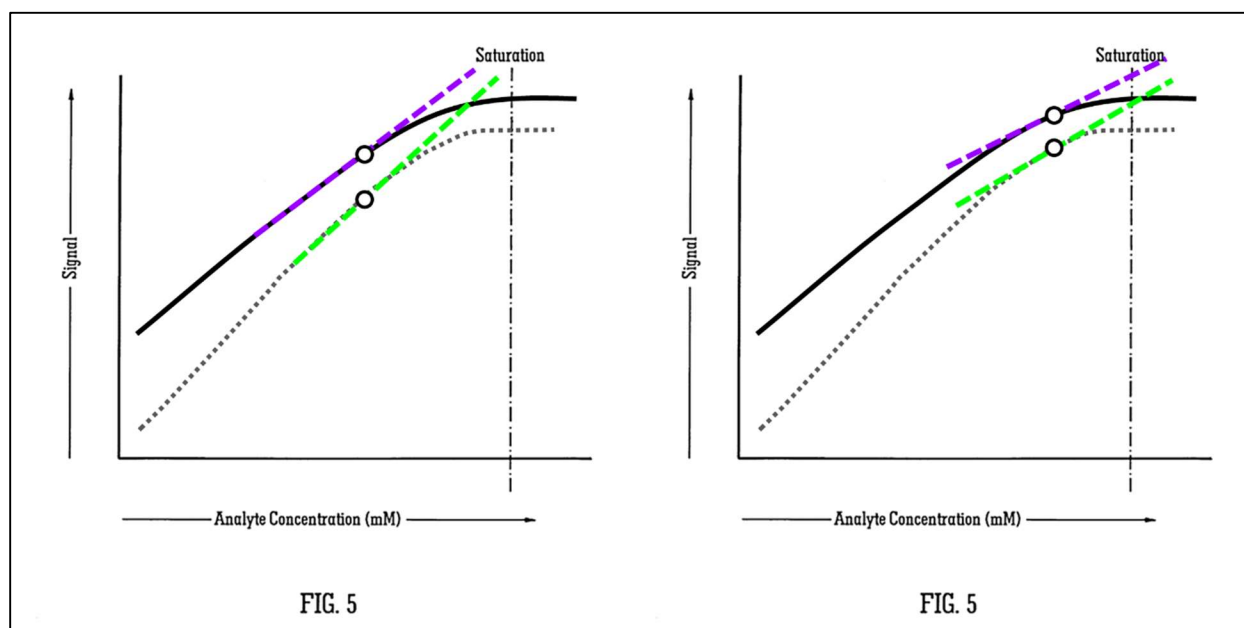
intermediate points on curve 42 (the points between the measured endpoints) from curve 40, based on the basic shape of curve 40; in other words, curve 40 is usable for the prediction of the shape of curve 42. In this way, Gross teaches a predictive relationship between both the points of theoretical (in-vitro) performance curve 40 and measured (in-vivo) performance curve 42, and the slopes of the curves. Ex-1004, 14:10-53; *see also* Ex-1004, 4:17-21.

98. The following annotated graphs illustrate the predictive relationship between in-vitro and in-vivo sensor sensitivity taught in Gross. Each graph below shows the tangent on in-vitro curve 40 (purple dashed line) and the tangent on in-vivo curve 42 (green dashed line), each tangent representing sensitivity at a particular analyte concentration. The second graph on the right below shows the tangents at a concentration corresponding to points 40c and 42c, and is the same graph provided above in the discussion of claim 1[b]:



99. As shown above in each graph, the slopes of the tangents (i.e., the sensitivities) differ from each other but are similar to each other, due to the similarity in shapes of curve 40 (in-vitro) and curve 42 (in-vivo).

100. The two graphs below show tangents on in-vitro curve 40 and in-vivo curve 42 at higher analyte concentrations:



101. At these concentrations too, the slopes of the tangents (i.e., the sensitivities) differ from, but are nevertheless similar to, each other. All four graphs above thus illustrate that, at various analyte concentrations, the in-vitro sensitivity (as represented by the slopes of the tangents of curve 40) is similar to and *predictive of* in-vivo sensitivity (as represented by the slopes of the tangents of curve 42), due to the similarity in basic shapes of curve 40 and curve 42.

102. Accordingly, because Gross teaches that in-vitro curve 40 is predictive of in-vivo curve 42 due to a relationship between the curves (they have the same basic shape), Gross also teaches that there is a relationship between the in-vitro sensitivity and the in-vivo sensitivity (the slopes of the tangents of the respective curves at a given glucose concentration) and that the in-vitro sensitivity is predictive of the in-vivo sensitivity due to such relationship.

5. 1[d]. “sensor electronics configured to be operably connected to the transcutaneous electrochemical glucose sensor;”

103. Claim 1[d] recites the term “operably connected.” The ’364 patent defines “operably connected” to refer to, without limitation, “one or more components being linked to another component(s) in a manner that allows transmission of signals between the components, e.g., wired or wirelessly.” Ex-1001, 12:43-50.

104. Gross discloses the element of claim 1[d].

105. Gross’s monitor device includes sensor electronics configured to be operably connected to the sensor. Gross’s monitor device includes a housing having first and second parts. Ex-1004, 9:50-52. The monitor device can include “reusable first part 12, which includes the electronic controlling circuitry, and disposable second part 13, which includes the enzymatic sensor needle 15.” Ex-1004, 10:62-65. The transcutaneous electrochemical sensor needle 15 is operably connected to the electronic controlling circuitry. Ex-1004, 9:64-10:9. *See also* Ex-1004, FIG. 1A (showing parts 12 and 13, and sensor needle 15), 18:59-64 (“The first part 12 and second part 13 are each provided with the requisite electrical connections (not shown) to connect the electrodes 15-17 to the electronic controlling circuitry provided in second part 13. Thus, the second part 13 can be a

reusable electronic controller module and first part 12 can be a disposable electrode module.”); *see also* Ex-1004, 4:41-57, 7:31-48.

6. 1[e]. “a processor configured to be operably connected to the sensor electronics;”

106. Gross discloses the element of claim 1[e].

107. Gross’s system includes a microprocessor. Gross’s microprocessor is labeled 18 in FIG. 1A. Ex-1004, 9:64-10:3. The microprocessor performs several functions, including measuring current (e.g., Ex-1004, 12:55-59), storing (in the microprocessor’s memory) sensor signals (Ex-1004, 13:3-29), and calibrating sensor data (Ex-1004, 14:5-53). For example, Gross explains that “the microprocessor 18 measures the current flowing through the circuit of which the working electrode 15 and the counter electrode 16 form a part thereof.” Ex-1004, 11:48-51. The microprocessor also monitors and records sensor signals as voltage is applied. Ex-1004, 13:3-41.

108. The microprocessor is operably connected to the sensor electronics. To perform the functions mentioned above, the microprocessor must be operably connected to the sensor electronics—i.e., the microprocessor must be linked to sensor electronics in a manner that allows the transmission of signals between the microprocessor and the sensor electronics (such signals including the sensor signals that are monitored and recorded by the microprocessor).

109. In addition, Gross explains that “[t]he electrodes 15, 16, 17 are connected to a microprocessor 18 via a voltage controller 19,” and that the microprocessor controls the voltages supplied by the voltage controller 19 to the electrodes. Ex-1004, 9:64-10:9. FIG. 1A shows a connection between the microprocessor 18 and the voltage controller 19, which in turn connects to sensor 15. Thus the microprocessor is operably connected to the sensor electronics. *See also* claim 1[d].

7. 1[f]. “a memory configured to be operably connected to the processor,”

110. Gross discloses the element of claim 1[f].

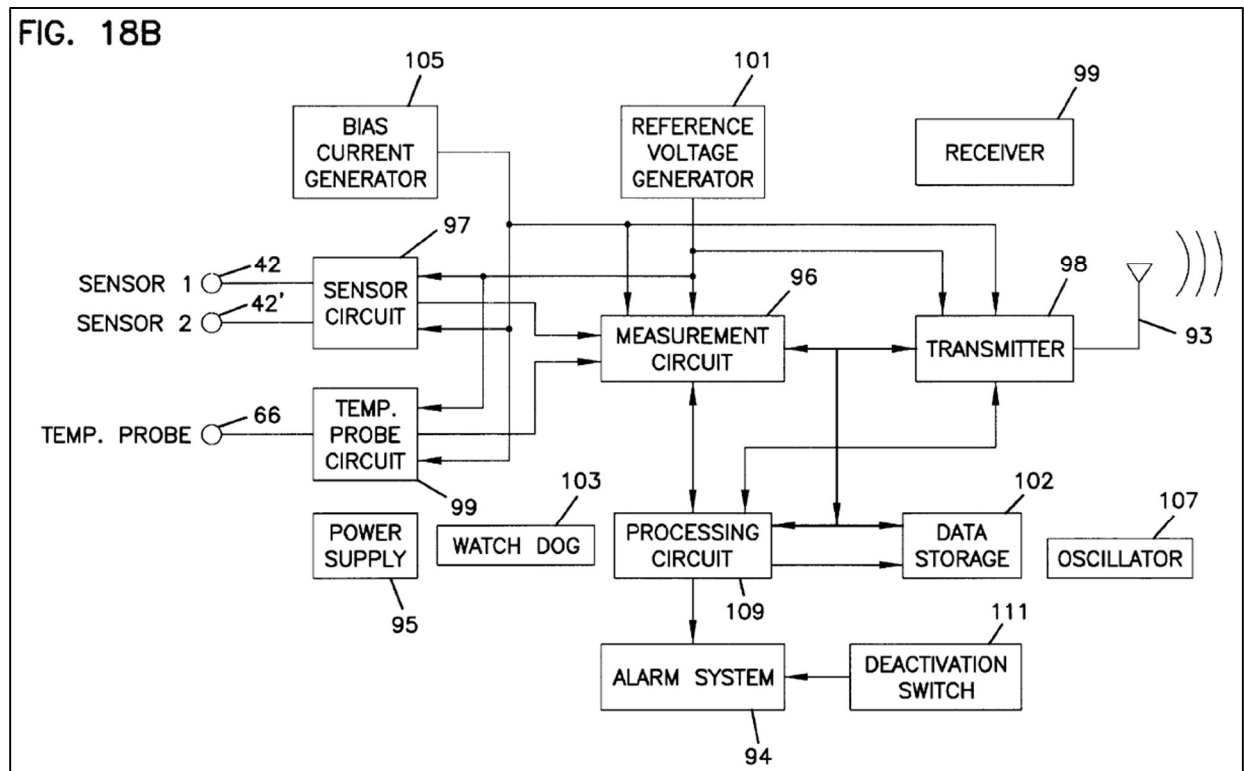
111. Gross’s system includes a memory, and the data and instructions for operation of the microprocessor, including instructions for calibrating sensor data, are stored in this memory. E.g., Ex-1004, 13:9-10, 14:19-53. Thus the memory is operably connected to the processor.

112. In addition, system components such as a memory operably connected to a processor were well-known in the art and were components common to many glucose monitoring systems described in the art. For example, Feldman (Ex-1005), Say (Ex-1011), and Mastrototaro (Ex-1010) all relate to glucose monitoring systems and describe system components and their configuration as recited in claim 1[f].

113. Feldman “relates to a method for calibrating an analyte-measurement device that is used to evaluate a concentration of analyte in bodily fluid” (Ex-1005, Abstract), including “a device that allows for the self-monitoring of glucose levels” (Ex-1005, ¶0019). Feldman in ¶0065 and FIG. 1B describes a glucose monitoring system that includes several elements, where the elements in turn can include “a signal- or data-processing element” and “storage media, such as temporary storage media or rewriteable storage media.” Feldman also teaches that the system includes a “microprocessor,” which is operably connected to other elements, such as the “calibration element” that includes “storage media.” Ex-1005, ¶0065. The microprocessor is labeled “118” in FIG. 1B. Feldman further discloses, in ¶0079, that a “calibration code” determined “at the site of manufacture” can be entered into “a data processor of the device” by “a manufacturer”—in other words, the data processor comprises, and thus is operably connected to, a memory that can store the calibration code that is entered by the manufacturer. Ex-1005, ¶0079.

114. Say also discloses a glucose monitoring system comprising a memory operably connected to a processor. Say describes a glucose monitoring system with an “on-skin sensor control unit” that can include “a calibration data storage unit” for storing calibration data. Ex-1011, 43:36-44, FIG. 18B. The “on-skin control unit” also includes a “processing circuit” (Ex-1011, 44:20-21), which may have a number of functions (Ex-1011, 39:61-40:27). As shown in FIG. 18B, the data

storage unit and processing circuit are operably connected to each other. *See also* Ex-1011, 44:54-45:7 (“The on-skin sensor control unit 44 may include an optional data storage unit 102 which may be used to hold data (e.g., measurements from the sensor or processed data) from the processing circuit 109 permanently or, more typically, temporarily. The data storage unit 102 may hold data so that the data can be used by the processing circuit 109”). FIG. 18B of Say is copied below:



115. Mastrototaro similarly discloses a glucose monitoring system comprising a memory operably connected to a processor. Mastrototaro describes a system comprising a “memory” and a “data processor,” and teaches that “[t]he memory values are retained in memory and may be downloaded to the data

processor 200.” Ex-1010, 8:56-58. Mastrototaro also teaches that “the data processor 200 may apply an algorithm to the sensor data” (Ex-1010, 8:24-26) and thereby teaches that the data processor contains memory to store the algorithm that is applied.

8. **1[g]. “wherein the memory has stored therein information associated with the in vivo sensitivity of the transcutaneous electrochemical glucose sensor, wherein the information associated with the in vivo sensitivity is based at least in part on corrections for the difference between the in vivo sensitivity and the in vitro sensitivity of the transcutaneous electrochemical glucose sensor.”**

116. Claim 1[g] recites the term “corrections for the difference between the in vivo sensitivity and the in vitro sensitivity” of the sensor. The term’s plain and ordinary meaning in light of the specification encompasses correcting for any difference in sensitivities in the in-vitro versus in-vivo environments.²

² There is no language in the claims themselves requiring that the “corrections for a/the difference” between sensitivities be corrections for the full difference between sensitivities. And neither the phrase “corrections for a/the difference,” nor any similar language relating to correcting for a difference between in-vitro sensitivity and in-vivo sensitivity, appears anywhere in the ’364 patent specification; thus the specification does not provide guidance on this claim element.

117. Gross discloses the element of claim 1[g].

118. In Gross, the information stored in the system's memory includes the "concentration-dependent calibration function" that is used to map in-vivo measured signals (lying on measured performance curve 42) to the theoretical performance curve (in-vitro curve 40) during use to provide a calibrated output in meaningful units. Ex-1004, 14:41-47. This calibration function is "information associated with the in vivo sensitivity" of the sensor, at least because such information "is based at least in part on corrections for the difference between the in vivo sensitivity and the in vitro sensitivity" of the sensor, as recited in claim 1[g].

119. As discussed above, Gross teaches that there can be a difference between the in-vivo and in-vitro sensitivities that characterize a sensor, as demonstrated by the difference in the slopes of curves 40 and 42 in FIG. 5. The difference in the slopes of curves 40 and 42 is a consequence of the difference between signals 40a and 42a being "considerably less" than the difference between signals 40b and 42b. Ex-1004, 14:39-41.

120. Gross's "concentration-dependent calibration function" corrects for the difference between curves 40 and 42, and therefore also for the difference in sensitivities defined by these curves. As Gross explains,

[T]he calibration function must take into account the fact that the difference between the saturation signals 40a, 42a is considerably less than the difference between the base line signals 40b, 42b. Thus, in order to map a measured point 42c onto the corresponding point 40c on theoretical curve 40, the microprocessor must apply a concentration-dependent calibration function in which the amount added to (or subtracted from) the measured signal 42c, when mapping this signal to point 40c, varies in accordance with the position of this point along curve 42c.

Ex-1004, 14:41-47. The concentration-dependent calibration function thus takes into account and corrects for differences between curve 40 (in-vitro) and curve 42 (in-vivo), including differences between the slopes, i.e., sensitivities, of these curves.

121. Accordingly, the concentration-dependent calibration function is “based at least in part on corrections for the difference between the in vivo sensitivity and the in vitro sensitivity,” and thereby also is information “associated with” the in-vivo sensitivity, as recited in claim 1[g]. Information (such as Gross’s concentration-dependent calibration function) that “is based at least in part on corrections for the difference between the *in vivo sensitivity* and the in vitro sensitivity” necessarily is information “*associated with* the in vivo sensitivity, as recited in claim 1[g]. In addition, because the conversion function (in this case,

Gross's concentration-dependent calibration function) encompasses calibration parameters including sensitivity, the conversion function (or Gross's concentration-dependent calibration function) is "information *associated with* the in vivo sensitivity."³

122. Gross also teaches that, once in-vivo saturation and baseline signals are recorded and the microprocessor calculates the calibration function (such as the concentration-dependent calibration function in the case of curve 42 based on curve 40), the microprocessor applies the calibration function to subsequently measured signals; thus the calibration function is stored in the system's memory. E.g., Ex-1004, 14:23-27 ("The calculation of a calibration function mapping curve 41 [or curve 42] onto curve 40 provides complete information for the

³ In reading claim 1 in the context of the patent specification, there is no requirement to calculate or determine a slope (sensitivity), in order to store "information associated with the in vivo sensitivity [that] is based at least in part on corrections for a difference between the in vivo sensitivity and an in vitro sensitivity" of the sensor. In other words, information can be "based at least in part on corrections for the difference between the in vivo sensitivity and the in vitro sensitivity," and also be "associated with" the in-vivo sensitivity, without an in-vivo sensitivity value being calculated.

microprocessor to provide a calibrated output for ***any subsequent measured signal*** which lies on curve 41 [or curve 42].”) (emphasis added).

B. Claim 2: “The glucose monitoring system of claim 1, wherein the relationship between the in vivo sensitivity and the in vitro sensitivity is established empirically by performing a clinical study and comparing in vivo sensitivities with in vitro sensitivities of a plurality of transcutaneous glucose sensors.”

123. Claim 2 recites that the in-vitro/in-vivo sensitivity relationship is established empirically by performing a clinical study of a plurality of sensors. I understand that, in a related litigation concerning the ’364 patent, Patent Owner (DexCom) has argued that claim 2 encompasses embodiments where the clinical study “of a plurality” of sensors is a clinical study involving *only* sensors *other than* the sensor in the claimed system (e.g., the clinical study is performed using sensors from the same batch as the sensor in the claimed system, but the study does not involve the sensor that is in the claimed system). I have applied Patent Owner’s interpretation of the scope of claim 2 in my analysis.

124. Gross discloses claim 2. Gross discloses establishing the sensitivity relationship (see claim 1) empirically in a clinical study as recited in claim 2. Gross alternatively renders obvious claim 2.

125. A clinical study is a study in humans. Clinical studies were and still are routinely performed in the art, during research and development and as part of

the regulatory or marketing approval process for devices such as CGMs. *See, e.g.*, Fraser at 37 (Ex-1013); Feldman-2003 (Ex-1006).

126. Gross expressly discloses examining in-vitro sensitivities of a plurality of sensors and that “it is known” that sensors from the same batch will have similarly shaped in-vitro and in-vivo calibration curves. Ex-1004, 14:10-15. The POSA would have understood that, to have such knowledge about the in-vitro/in-vivo calibration curves, a study examining sensor performance in vivo (i.e., a clinical study) necessarily had to have been performed. In addition, the POSA would have found it obvious to have performed such a clinical study, to be able to compare sensor in-vivo and in-vitro performance and acquire the knowledge expressly disclosed in Gross.

127. Specifically, Gross teaches determining sensor in-vitro sensitivity by examining a plurality of sensors (of a given batch) at the factory, and applying that in-vitro sensitivity determination to all sensors in the batch. Gross teaches determining, at the factory, the in-vitro performance curve (e.g., theoretical performance curve 40 in FIG. 5) for a batch of sensors “by taking a statistically representative sample of needles from a production batch, carrying out a laboratory calibration (using a standard glucose solution, for example) and applying the results of this calibration for all of the needles in the batch.” Ex-1004, 12:30-37; *see also* Ex-1004, 13:46-48 (“Curve 40 is the theoretical or laboratory-calibrated

performance curve measured in the manufacturing facility for the batch of sensor needles.”), 4:9-12 (“The theoretical sensor performance curve can be determined during the design of the sensor, can be measured for individual sensors during production, or can be measured for a manufactured batch of sensors on a statistical basis.”).

128. Gross further teaches that the sensors in the batch are intended to be used in vivo (in a host), and that once inserted into a host, each sensor’s in-vivo performance curve is expected to have the same basic shape as the pre-determined in-vitro performance curve. Ex-1004, 14:10-15 (“[I]t is known that the calibration curves for needles from the same batch will all have the same basic shape....”); *see also* Ex-1004, 4:9-16 (“Two curves having basic common parameters (such as a common shape) can thus be correlated to one another by comparing known points on each curve and extrapolating for subsequently measured points.”).

129. Gross thus teaches *prior knowledge* that the in-vitro and in-vivo performance curves will have the same basic shape; and as discussed above, these curves include information on sensor sensitivity in the in-vitro or in-vivo environments.

130. The POSA would have reasonably understood that this knowledge—that the in-vivo curve will have the same basic shape as the in-vitro curve for sensors from the same batch—was determined empirically; further, examining in-

vivo sensor performance empirically necessarily would have entailed a clinical study. Thus, by teaching that “it is known” that the in-vitro and in-vivo performance curves “for needles from the same batch will all have the same basic shape” (Ex-1004, 14:10-11), Gross discloses that the relationship between in-vivo and in-vitro sensor performance (i.e., the relationship between curve 40 and curve 42, that the curves have a similarity in basic shape), and thus between in-vivo sensitivity and in-vitro sensitivity, is established empirically by performing a clinical study and comparing sensor performance (and thus also in-vivo sensitivities with in-vitro sensitivities) of a plurality of sensors, as recited in claim 2.

131. Claim 2 also would have been obvious based on the teachings of Gross and the knowledge in the art of how glucose sensors were and still are routinely characterized and studied.

132. For example, the POSA would have been familiar with research conducted in the field, where glucose monitoring systems comprising transcutaneous electrochemical sensors were routinely tested in vitro (as is also expressly disclosed in Gross) and in humans to, among other things, examine and compare sensor performance in the in-vitro and in-vivo environments. Feldman-2003 (Ex-1006) and Nishida (Ex-1007) are examples of such routine testing conducted in the art. Both Feldman-2003 and Nishida describe in-vitro testing and

in-vivo human (i.e., clinical) studies of transcutaneous electrochemical glucose sensors. E.g., Feldman-2003 at 772-779 (Ex-1006); Nishida at 94-102 (Ex-1007).

133. Given that testing sensors in vitro (such as in the laboratory) and in vivo (in clinical studies) was standard practice in the art, as a routine step in characterizing sensors and as part of the marketing approval process, the POSA would have had reason to conduct such routine testing, including for sensors used in the systems disclosed in Gross. In other words, the POSA would have had reason to examine the in-vitro/in-vivo sensitivity relationship of sensors empirically, through a clinical trial, at least because such testing was standard, routine practice in the art for sensors under development as of the asserted priority date.

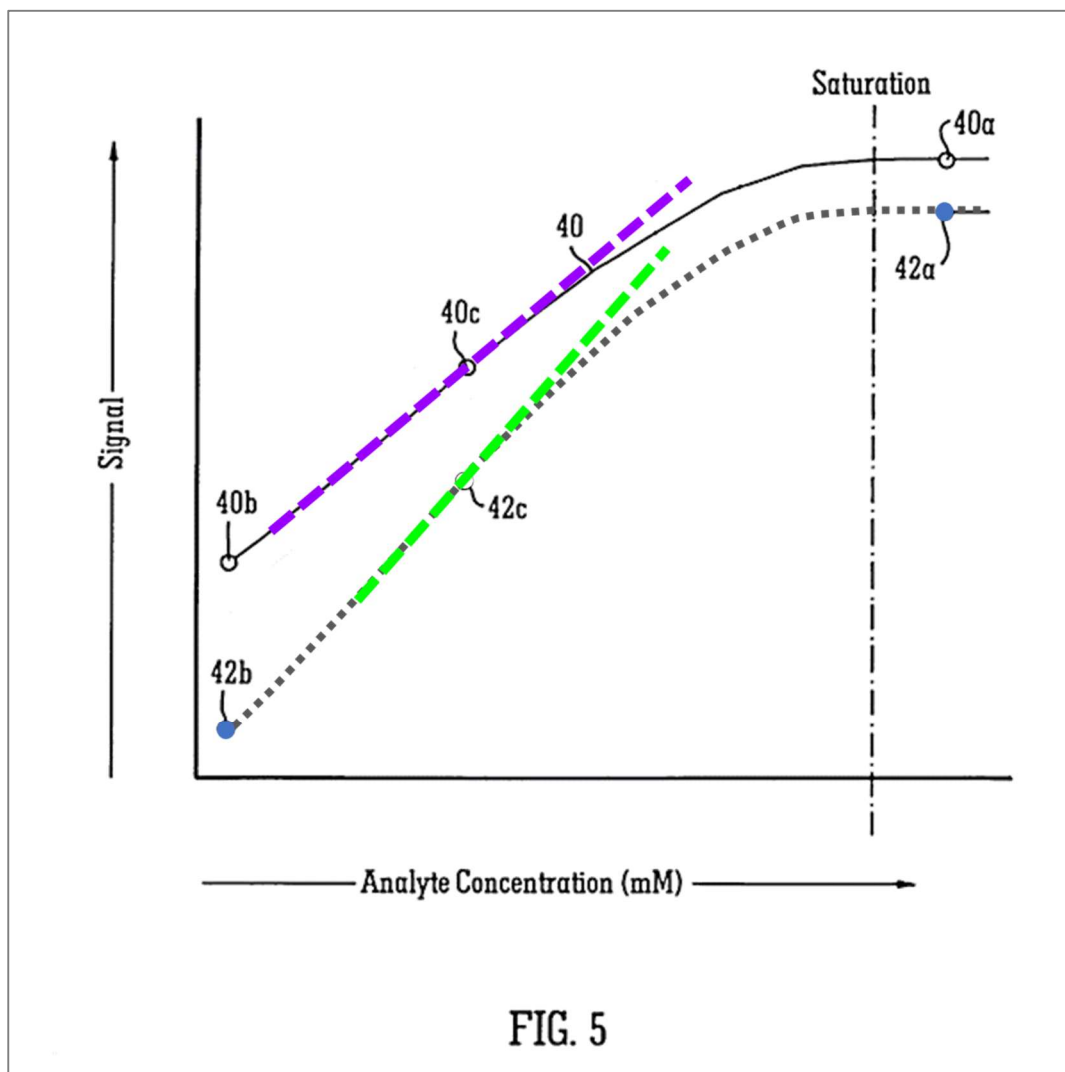
C. Claim 3: “The glucose monitoring system of claim 1, wherein the in vivo sensitivity is greater than the in vitro sensitivity.”

134. Gross discloses claim 3.

135. Gross teaches an in-vivo sensitivity that is greater than the in-vitro sensitivity for the sensor having in-vivo curve 42 shown in FIG. 5. Especially at low glucose concentrations, the slope of the tangent on in-vivo curve 42 is greater than the slope of the tangent on in-vitro curve 40, and therefore the in-vivo sensitivity is greater than the in-vitro sensitivity at these glucose concentrations. *See also* claim 1[b], ¶¶ 89-93 above.

136. As explained above, in a plot of analyte concentration on the x-axis and sensor signal on the y-axis (as in Gross's FIG. 5), sensor sensitivity corresponds to the slope of the curve (e.g., the slope of the tangent on a point on the curve).

137. Annotated FIG. 5 below shows the tangent (green dashed line) at point 42c on in-vivo curve 42, and the tangent (purple dashed line) at corresponding point 40c on in-vitro curve 40. The slope of the tangent at point 42c (i.e., the slope of the green dashed line) is higher or greater than the slope of the tangent at point 40c (i.e., the slope of the purple dashed line):



138. The '364 patent at 81:5-6 acknowledges that a higher slope equates to a higher sensitivity, and that a lower slope equates to a lower sensitivity, as the patent recites “higher slope (sensitivity)” and “lower slope (sensitivity)” when discussing regression lines calculated from a plot of “matched data pairs” of “sensor data and time-correspondence reference glucose data.” Ex-1001, 80:50-81:7.

139. Gross therefore teaches a sensor characterized by an in-vivo sensitivity and an in-vitro sensitivity, wherein the in-vivo sensitivity is greater than the in-vitro sensitivity, as required by claim 3 of the '364 patent.

D. Independent Claim 5

1. 5[Pre]. “A method for calibrating data from a transcutaneous electrochemical glucose sensor, the method comprising:”

140. To the extent the preamble is limiting, it is disclosed in Gross.

141. Gross teaches “a method of calibrating an analyte sensor,” where “a particularly preferred analyte is glucose.” Ex-1004, 4:24-40.

142. In addition, as discussed above for claim 1[a], Gross’s calibration method is for “a transcutaneous electrochemical glucose sensor.” *See* ¶¶84-88, above.

2. 5[a]. “receiving sensor data from the transcutaneous electrochemical glucose sensor after at least a portion of the transcutaneous electrochemical glucose sensor is inserted in a host, wherein the sensor data is indicative of a glucose concentration in the host;”

143. Gross discloses the element of claim 5[a].

144. Gross teaches that the sensor output received after sensor insertion into the host corresponds to a glucose concentration in the host. Ex-1004, 10:60-12:24; *see also* Ex-1004, 1:12-26; e.g., Ex-1004, 1:23-24 (“The level of concentration of glucose is proportional to the magnitude of the current.”).

145. Gross explains that, “when a voltage is applied to the working electrode 15, the microprocessor 18 measures the current flowing through the circuit of which the working electrode 15 and the counter electrode 16 form a part thereof.” Ex-1004, 11:48-51. Gross further teaches that this current measured by the microprocessor is indicative of a glucose concentration in the host. The current measured is based on the amount of hydrogen peroxide produced at the surface of the needle, and the amount of hydrogen peroxide produced in turn depends on, and therefore is indicative of, the concentration of glucose present in the host. Ex-1004, 11:10-34.

146. Specifically, Gross explains that “glucose in the blood, plasma or serum present in the subcutaneous region” diffuses to the sensor needle and reacts with oxygen and water in the presence of glucose oxidase, producing hydrogen peroxide at sensor needle 15, and that “the rate of hydrogen peroxide generation at platinum-iridium needle 15 is theoretically proportional to the concentration of glucose in the bloodstream.” Ex-1004, 11:11-23.

3. 5[b]. “and calibrating, using a processor, the sensor data received from the transcutaneous electrochemical glucose sensor,”

147. Gross discloses the element of claim 5[b]. Gross’s method involves calibrating sensor data, and Gross teaches using a processor to perform the calibration.

148. As discussed above, Gross's system stores information (e.g., the measured performance curve 42) and uses this information to calculate a concentration-dependent calibration function that is then also stored and applied to subsequently measured signals, to calibrate those signals and generate calibrated output. Ex-1004, 14:10-53; *see also* Ex-1004, 8:31-42. Such calibration is performed by a processor. E.g., Ex-1004, 14:19-47 (explaining how the microprocessor provides a calibrated output for subsequently measured signals that lie on a measured (in-vivo) performance curve). See also discussions above for claim 1[e], 1[f], 1[g], in ¶¶106-122 above.

149. Specifically, when the microprocessor receives sensor data, the microprocessor uses the calibration function to determine the corresponding point on the in-vitro curve (theoretical performance curve 40) and transmits the calibrated output to the display unit. Ex-1004, 14:19-53. As Gross explains:

[W]hen a signal 41c is measured, the microprocessor calculates the corresponding point 40c and provides, as an output which is transmitted to the display unit, the calibrated measurement corresponding to point 40c which can then be displayed in meaningful units. The same basic principles apply to the calibration of the individual sensor needle which has characteristic measured curve 42.

Ex-1004, 14:31-38.

150. Gross also describes the calibration method at 8:33-41:

[T]he calibration function correlates the measured performance curve with a theoretical sensor performance curve for which there is stored a calibrated output, such that any further sensor signal measurement from the sensor can be calibrated by correlating the point on the measured performance curve to which the measurement relates with a corresponding point on the theoretical sensor performance curve, and hence with the corresponding calibrated output.

Ex-1004, 8:33-41.

151. Accordingly, in the case of curve 40 and curve 42 and the concentration-dependent calibration function, the microprocessor applies the concentration-dependent calibration function to sensor data, to calculate the corresponding point on the in-vitro curve (theoretical performance curve 40) and then transmits the calibrated output to the display unit. Gross thus discloses calibrating, using a processor, the sensor data received from the sensor after sensor insertion.

4. **5[c]. “wherein the calibrating is based at least in part on information associated with an in vivo sensitivity of the transcutaneous electrochemical glucose sensor, wherein the information associated with the in vivo sensitivity is based at least in part on corrections for a difference between the in vivo sensitivity and an in vitro sensitivity for the transcutaneous electrochemical glucose sensor.”**

152. Gross discloses the element of claim 5[c]. Gross’s calibration method discussed above for claim 5[b] “is based at least in part on information associated with an in vivo sensitivity” of the sensor because such information is in turn “based at least in part on corrections for a difference between the in vivo sensitivity and an in vitro sensitivity” for the sensor, as recited in claim 5[c].

153. As discussed above, Gross’s calibration method employs a calibration function. Ex-1004, 14:10-53. The calibration function constitutes information “*associated with* an in-vivo sensitivity,” at least because the calibration function corrects for a difference between in-vitro and in-vivo sensitivities. How the calibration function corrects for a difference between the in-vivo sensitivity and the in-vitro sensitivity was discussed above for claim 1[g] (*see* ¶¶ 119-122 above) and is also explained below.

154. In addition, because applying the calibration function to sensor data corrects for a difference between in-vivo sensitivity and in-vitro sensitivity, the calibration function also is information “based at least in part on corrections for a

difference between the in vivo sensitivity and an in vitro sensitivity,” as recited in claim 5[c].

155. Applying the calibration function to sensor data corrects for a difference between the in-vivo sensitivity and the in-vitro sensitivity, because the calibration function maps intermediate points on in-vivo curve 42 to the corresponding points on in-vitro curve 40 and thereby corrects for a difference between these curves. Ex-1004, 14:36-47. In correcting for a difference between the curves, the calibration function also corrects for a difference in the sensitivities underlying these curves, as the function defining each curve includes sensitivity.

156. Specifically, and as explained above for claim 1[g], each of these curves (in-vivo curve 42 and in-vitro curve 40) defines sensor sensitivity. For example, the measured (in-vivo) performance curve 42 defines sensor in-vivo sensitivity: the slope of the tangent on curve 42, at a given analyte (e.g., glucose) concentration, is sensor in-vivo sensitivity at that analyte concentration. The same principle applies for curve 40.

157. In addition, each of these curves (in-vivo curve 42 and in-vitro curve 40) is associated with different sensitivities; the slopes of the tangents of these curves are different from each other over a range of analyte (e.g., glucose) concentrations (including the concentration corresponding to points 42c and 40c).

158. Accordingly, when Gross provides calibrated output, Gross's calibration function corrects for the difference between in-vivo curve 42 and in-vitro curve 40 and by doing so corrects for the difference in sensitivities that are defined by these curves.

E. Claim 6: "The method for calibrating data from a transcutaneous electrochemical glucose sensor of claim 5, wherein the calibrating requires no user calibrations after the at least a portion of the transcutaneous electrochemical glucose sensor is inserted in the host."

159. Gross discloses claim 6.

160. Gross's calibration method does not require any user calibrations after the sensor is inserted into the host. The microprocessor calculates the calibration function based on a theoretical (in-vitro) performance curve (for example, a laboratory-measured curve such as a curve determined at the factory), and a measured (in-vivo) performance curve determined by the system when the needle 15 enters the body, without any user measurements. Ex-1004, 12:55-13:41.

161. Specifically, Gross's system initiates a process for obtaining and recording saturation and baseline signals and then generating a measured (in-vivo) performance curve and calculating a calibration function to be used for calibrating subsequently measured sensor signals. E.g., Ex-1004, 12:55-13:26 (explaining how the microprocessor controls the process for obtaining and recording saturation and baseline signals I_1 and I_9 "for calibration purposes"), 14:5-9 (explaining that the

microprocessor “compares” the recorded saturation and baseline signals “with the corresponding signals on the theoretical or laboratory-measured signal-concentration curve 40” to generate “a calibration function”), 14:10-53 (explaining how the system calibrates sensor data, without user intervention). The calibration process is run by the microprocessor and does not rely on or require any user calibrations.

F. Claim 8: “The method for calibrating data from a transcutaneous electrochemical glucose sensor of claim 5, wherein the in vitro sensitivity for the transcutaneous electrochemical glucose sensor is based at least in part on sampling a plurality of transcutaneous electrochemical glucose sensors prior to inserting the at least a portion of the transcutaneous electrochemical glucose sensor in the host.”

162. Gross discloses claim 8.

163. Gross teaches examining the in-vitro sensitivity by sampling a plurality of sensors prior to sensor insertion in the host. Gross teaches that the calibration process includes determining, at the factory, the in-vitro curve “by taking *a statistically representative sample of needles* from a production batch, carrying out a laboratory calibration (using a standard glucose solution, for example) and applying the results of this calibration for all of the needles in the batch.” Ex-1004, 12:30-37 (emphasis added); *see also* Ex-1004, 13:46-48 (“Curve 40 is the theoretical or laboratory-calibrated performance curve measured in the manufacturing facility for the batch of sensor needles.”). As explained above, the

in-vitro curve defines in-vitro sensitivity. *See* ¶¶33-39 and claim 1[b], ¶¶90-91 above.

164. To the extent Gross is understood as teaching that the “statistically representative sample of needles from a production batch”—i.e., the plurality of sensors—excludes the sensor that is part of the claimed system, Gross still teaches a system as recited in claim 8 under Patent Owner’s interpretation of the claim. I understand that Patent Owner, in the co-pending court proceeding, has interpreted claim 8 as encompassing embodiments where the recited “plurality” of sensors excludes the sensor that is part of the claimed system and includes only other sensors. I have applied Patent Owner’s interpretation of claim 8 for the purpose of my analysis. The same applies to claim 9 below.

G. Claim 9: “The method for calibrating data from a transcutaneous electrochemical glucose sensor of claim 8, wherein the in vitro sensitivity is calculated at least in part by examining a signal response of each of the plurality of transcutaneous electrochemical glucose sensors to a set of known glucose concentrations.”

165. Gross discloses claim 9, and in the alternative renders obvious claim 9.

166. As explained above for claim 8, Gross teaches examining the in-vitro sensitivity by sampling a plurality of sensors prior to sensor insertion in the host. Gross further teaches calculating in-vitro sensitivity by examining each of the plurality of sensors using “a set of known glucose concentrations,” as recited in

claim 9. Claim 9 also would have been obvious based on Gross and the POSA's knowledge of the typical, in-vitro characterization testing of glucose sensors that researchers conducted in the field.

167. Gross teaches that the laboratory calibration (see discussion of claim 8 above) is performed by measuring sensor response “using a standard glucose solution, for example.” Ex-1004, 12:30-37. An example in-vitro curve is shown in FIG. 5, which in turn shows at least two sensor signal measurements, 40b and 40a. E.g., Ex-1004, 14:5-9 (referring to signal 40a and signal 40b on the “laboratory-measured signal-concentration curve”). 40a is the in-vitro saturation signal and 40b is the in-vitro baseline signal. Ex-1004, 14:38-41. Thus the “set of known glucose concentrations” in Gross includes at least a concentration corresponding to saturation, and a concentration (which could be zero) corresponding to baseline. *See also* Ex-1004, 1:33-41 (calibrating a sensor can include measuring a “standard solution of the analyte for which they are intended, and thereby determining the signal strength achieved from a known concentration of analyte”).

168. Claim 9 also would have been obvious based on Gross and the POSA's knowledge of how sensors were routinely characterized in vitro.

169. Calculating in-vitro sensitivity at least in part by examining sensor signal response to a set of known glucose concentrations would have been obvious, at least because doing so was standard, routine practice and was part of the typical

in-vitro testing researchers conducted to characterize sensors in the in-vitro environment.

170. That calculating in-vitro sensitivity as recited in claim 9 was routine is evidenced by studies reported in the literature, including Velho, Nishida, Feldman, and Ward.

171. Velho describes examining sensors in vitro, to determine their in-vitro characteristics including sensitivity. The sensors were tested in a buffered solution “during stepwise increases of the glucose concentration from 0 to 30 mmol/l.” Velho at 959 (Ex-1008). *See also* Velho at 960 (Ex-1008) (Table 1); Velho at 961 (Ex-1008) (Fig. 4, showing that four glucose concentrations were used to determine the in-vitro calibration curve).

172. Nishida reports the in-vitro and in-vivo characteristics of a needle-type glucose sensor. Nishida explains that “the in vitro characteristics of the sensor were assessed by placing the sensor in saline solution with varying glucose concentrations (0-27.8 mmol/l) in a temperature-controlled (37 °C) chamber.” Nishida at 94 (Ex-1007). Five sensors were tested, and results are reported in Table 1. Nishida at 96 (Ex-1007) (Table 1).

173. Feldman-2003 reports the results of an in-vitro test, examining sensor output of eight sensors “over the glucose concentration range 20-500 mg/dL” and under two different oxygen levels, to “determine the effect of oxygen on the

sensor's linearity." Feldman-2003 at 774 (Ex-1006) (FIG. 4). "The results are shown in Figure 4, a plot of current versus glucose concentration," where "[b]oth high and low oxygen curves exhibit excellent linearity ... over the glucose range from 18 to 540 mg/dL," and "[t]he difference in slope is only 4%." Feldman-2003 at 774 (Ex-1006).

174. Ward reports a study comparing sensors fabricated by an "original protocol" to sensors fabricated by a "revised protocol." Ward characterizes both types of sensors in vitro and in animals. "All sensors had sensitivity measured as the rise in sensor output per unit rise in glucose as glucose was raised from 0 to 5 mM." Ward at 184 (Ex-1009). "Sensor output was measured at multiple glucose levels (0, 5, 10, 15, and 20 mM) in many sensors (of intermediate sensitivity) in both groups in order to assess linearity." Ward at 184 (Ex-1009). *See also* Ward at 186 (Ex-1009) (FIG. 4, reporting results, in a plot of sensor output (nA) versus glucose level in vitro (mM), of eight sensors during continuous polarization, and noting "[n]o significant change in slope (sensitivity)" was observed on certain days; at least four glucose levels were tested).

175. As demonstrated by the studies discussed above, testing sensor response to a series of glucose concentrations was part of the typical, in-vitro characterization of sensors that researchers conducted in the field. Testing sensor response to multiple glucose concentrations, as was done in the above studies, and

consequently having a number of matched pairs from which to empirically derive the in-vitro conversion function, increased the accuracy of the empirically-derived in-vitro conversion function and the sensitivity determination. Furthermore, testing sensors in vitro, using multiple glucose concentrations, was well within the skill of researchers working in the field, as evidenced by the studies discussed above.

H. Independent Claim 10

1. **10[Pre]. “A method for providing calibrated glucose information based on sensor data from a transcutaneous electrochemical glucose sensor, the method comprising:”**

176. To the extent the preamble is limiting, Gross discloses it.

177. Gross’s method provides “calibrated glucose information based on sensor data,” as recited in the preamble of claim 10. E.g., Ex-1004, 14:23-27 (“The calculation of a calibration function mapping curve 41 onto curve 40 provides complete information for the microprocessor to *provide a calibrated output* for any subsequent measured signal which lies on curve 41.”) (emphasis added), 14:30-35, 14:36-38 (same principles apply to curve 42). See discussions above for claim 5[pre], 5[b], in ¶¶140-142 and ¶¶147-151 above.

2. **10[a]. “receiving, by a processor, post-implantation sensor data from the transcutaneous electrochemical glucose sensor, wherein the sensor data is indicative of a glucose concentration in a host;”**

178. Gross discloses the element of claim 10[a].

179. Gross teaches that the microprocessor measures the current after the sensor needle 15 (which Gross also refers to as “working electrode 15,” Ex-1004, 11:33) is inserted into the host. Ex-1004, 10:60-11:57. “[W]hen a voltage is applied to the working electrode 15, the microprocessor 18 measures the current flowing through the circuit of which the working electrode 15 and the counter electrode 16 form a part thereof.” Ex-1004, 11:48-51. This current is “post-implantation sensor data” received by a processor “from the transcutaneous electrochemical glucose sensor,” as recited in claim 10[a].

180. Gross further teaches that this current measured by the microprocessor is indicative of a glucose concentration in the host. The current measured is based on the amount of hydrogen peroxide produced at the surface of the needle, and the amount of hydrogen peroxide produced in turn depends on, and therefore is indicative of, the concentration of glucose present in the host. Ex-1004, 11:10-34. Gross explains that “glucose in the blood, plasma or serum present in the subcutaneous region” diffuses to the sensor needle and reacts with oxygen and water in the presence of glucose oxidase, producing hydrogen peroxide at sensor needle 15, and that “the rate of hydrogen peroxide generation at platinum-iridium needle 15 is theoretically proportional to the concentration of glucose in the bloodstream.” Ex-1004, 11:11-23.

3. **10[b]. “receiving, by the processor, information associated with an in vivo sensitivity of the transcutaneous electrochemical glucose sensor, wherein the information associated with the in vivo sensitivity is based at least in part on corrections for a difference between the in vivo sensitivity and an in vitro sensitivity for the transcutaneous electrochemical glucose sensor;”**

181. Gross discloses the element of claim 10[b]. In Gross’s calibration method, the processor receives information associated with an in-vivo sensitivity of the sensor, “wherein the information associated with the in vivo sensitivity is based at least in part on corrections for a difference between the in vivo sensitivity and an in vitro sensitivity for the transcutaneous electrochemical glucose sensor,” as recited in claim 10[b].

182. To calibrate sensor data for a sensor having measured (in-vivo) performance curve 42, Gross’s method applies a concentration-dependent calibration function that maps the sensor data to theoretical performance curve 40. *See* claim 5[b]. Thus, to provide calibrated glucose information to the user, the processor receives and uses the calibration function to calibrate the sensor data.

183. This concentration-dependent calibration function is “information associated with an in vivo sensitivity” of the sensor that is “based at least in part on corrections for a difference between the in vivo sensitivity and an in vitro sensitivity,” as explained above for claim 1[g] and 5[c]. *See* ¶¶116-122 and ¶¶152-158 above. Accordingly, because Gross’s microprocessor receives and uses the

calibration function when providing calibrated glucose information based on sensor signals lying on the intermediate points of curve 42, Gross's microprocessor receives and uses "information associated with an in vivo sensitivity" of the sensor that is "based at least in part on corrections for a difference between the in vivo sensitivity and an in vitro sensitivity," as recited in claim 10[b].

4. **10[c]. "generating calibrated sensor data, using the processor, by using the information associated with the in vivo sensitivity of the transcutaneous electrochemical glucose sensor to calibrate the sensor data received from the transcutaneous electrochemical glucose sensor;"**

184. Gross discloses the element of claim 10[c].

185. In Gross's method, the microprocessor generates calibrated sensor data by using the concentration-dependent calibration function to calibrate the data received from the sensor, as explained above for claim 5[b] and 5[c]. Specifically, the microprocessor uses the concentration-dependent calibration function to map sensor data (measured signals corresponding to intermediate points on curve 42) to corresponding points on theoretical curve 40 and thereby calibrate the sensor data. Ex-1004, 14:10-53. As explained above, the concentration-dependent calibration function is information associated with the in-vivo sensitivity of the sensor, as recited in claim 10[c]. *See* claim 1[g], 5[b], 5[c], and 10[b], discussed respectively in ¶¶116-122, ¶¶147-151, ¶¶152-158, and ¶¶181-183, above.

5. 10[d]. “and providing the calibrated sensor data to a user to facilitate monitoring a glucose level of the host.”

186. Gross discloses the element of claim 10[d].

187. The purpose of Gross’s system and method is to provide calibrated sensor data to the user, so that the user can meaningfully monitor his/her glucose level. E.g., Ex-1004, 15:5-20. To this end, Gross teaches a display unit that includes a visual LCD display. Ex-1004, 10:10-14. The display unit provides “a visual output of the measured analyte levels.” Ex-1004, 9:48-49. Gross explains that “the microprocessor calculates the corresponding point 40c and provides, as an output which is transmitted to the display unit, the calibrated measurement corresponding to point 40c which can then be displayed in meaningful units.” Ex-1004, 14:30-35. By providing, as a visual output on the display unit, “the calibrated measurement” of glucose levels “displayed in meaningful units,” Gross teaches the element of claim 10[d].

XI. AVAILABILITY FOR CROSS-EXAMINATION

188. In signing this declaration, I recognize that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross-examination in the case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for

cross-examination within the United States during a time as mutually agreed
between Patent Owner and Petitioner.

XII. RIGHT TO SUPPLEMENT

189. This declaration represents only those opinions that I have formed to date. I reserve the right to supplement my opinions in the future to respond to any arguments that the Patent Owner or its expert raises. I reserve the right to revise, supplement, and/or amend my opinions stated herein based on new information that becomes available to me and on my continuing analysis of the materials already provided.

XIII. CONCLUSION

190. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: April 26, 2024

Respectfully submitted,

By: A. Cass
Professor Anthony Edward George Cass

APPENDIX A

PROFESSOR ANTHONY EDWARD GEORGE CASS FRSC, CChem, FRSB, MIET

CURRENT POST: Professor Emeritus in Analytical Chemistry and Senior Research Investigator, Department of Chemistry Imperial College London.

Previous Positions:

- 2018-2023, Director of the Agilent Measurement Suite, Imperial College London.
- 2005-2010, Deputy Director, Institute of Biomedical Engineering, Imperial College
- 2001-2005, Professor of Chemical Biology, Department of Biological Sciences, Imperial College
- 1994-2001, Reader in Bioanalytical Chemistry, Department of Biochemistry, Imperial College London
- 1988-1994, Senior Lecturer, Department of Biochemistry, Imperial College London
- 1983-1988, Lecturer and Deputy Director, Centre for Biotechnology, Imperial College London
- 1980-1983, British Petroleum Junior Research Fellow, St Hugh's College, Oxford
- 1978-1980, Post-Doctoral Research Assistant, Inorganic Chemistry Laboratory, University of Oxford
- 1975-1978, Hastings Senior Scholar. The Queen's College, Oxford
- 1974-1975, Research Technician, Chemistry Department, University of York

Research Areas:

- Minimally invasive microneedle biosensors for continuous monitoring of drugs, metabolites and hormones in animals and humans
- Nucleic acid aptamers for sensing and imaging
- Point of care diagnostics based on novel lateral flow assay formats.
- Molecular Sensors for environmental pollutants

Degrees and Fellowships:

- 1971-1974, B.A. (Hons) 1st Class in Chemistry University of York
- 1975-1978, D.Phil. Inorganic Chemistry, University of Oxford
- Fellow of the Royal Society of Chemistry
- Fellow of the Royal Society of Biology

Visiting Chairs:

Chinese Academy of Sciences, Universiti Teknologi Malaysia, University of Rome La Sapienza, University of Bari, Italy

Awards:

- Royal Society-Mullard Medal (1994)
- Royal Society of Chemistry-Chemical Landmark Award (2012)
- Royal Society of Chemistry Sir George Stokes Award (2017)

Advisory Board Memberships & Commercial Interactions:

- *Technical University of Eindhoven, Dept. of Biomedical Engineering*
(International Advisory Board)
- *Jagellonian University, Krakow, Poland. Malopolska Biotechnology Centre*
(International Advisory Board)
- *Bionano Consulting Ltd* (Co-Founder, Director)
- *AquAffirm Ltd* (Co-Founder, Director)

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