

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. IPR2024-00891
Patent No. 11,020,031

**DECLARATION OF DR. ANTHONY EDWARD CASS IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 11,020,031**

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LIST OF EXHIBITS

Exhibit No.	Description of Exhibit
1001	U.S. Patent No. 11,020,031 (“’031 patent”)
1003	Prosecution File History of U.S. Patent No. 11,020,031
1004	Zhang et al., <i>System and Method for Sensor Recalibration</i> , U.S. Patent Application Publication No. 2005/0143636 (published June 30, 2005) (“ Zhang ”)
1005	David A. Gough, <i>Method and Membrane Applicable to Implantable Sensor</i> , U.S. Patent No. 4,650,547 (issued Mar. 17, 1987)
1006	David A. Gough et al, <i>Complete Glucose Monitoring Systems with an Implantable, Telemetered Sensor Module</i> , U.S. Patent No. 4,703,756 (issued Nov. 3, 1987)
1007	Wayne A. Morgan et al., U.S. Patent Application Publication No. 2003/0076082, <i>Implantable Sensor Electrodes and Electronic Circuitry</i> (published Apr. 24, 2003) (“ Morgan ”)
1008	John J. Shin et al., <i>Real Time Self-Adjusting Calibration Algorithm</i> , U.S. Patent Application Publication No. 2005/0004439 (published Jan. 6, 2005) (“ Shin ”)
1009	John J. Mastrototaro et al., <i>Glucose Sensor</i> , U.S. Design Application No. 29/101,218 (U.S. Design Patent D433,755, issued Nov. 14, 2000) (the “ 218 application ”)
1010	John J. Mastrototaro et al., <i>Glucose Monitor Calibration Methods</i> , U.S. Patent No. 6,424,847 (issued July 23, 2002) (“ Mastrototaro ”)
1011	James 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	Benjamin J. Feldman et al., <i>A Method of Calibrating an Analyte-Measurement Device, and Associated Methods, Devices and Systems</i> , U.S. Patent Application Publication No. 2005/0239154 (published Oct. 27, 2005 (“ Feldman ”))
1013	William Peter Van Antwerp et al., <i>Hydrophilic, Swellable Coatings for Biosensors</i> , U.S. Patent No. 5,786,439 (issued July 28, 1998) (“ Van Antwerp ”))
1014	Marc D. Breton et al., <i>Method, System and Computer Program Product for Real-Time Detection of Sensitivity Decline in Analyte Sensors</i> , U.S. Patent Application Publication No. 2008/0172205 (published July 17, 2008) (“ Breton ”))
1015	John P. Willis, <i>Biofouling Self-Compensating Biosensor</i> , U.S. Patent Application Publication No. 2007/0299617 (published Dec. 27, 2007) (“ Willis ”))
1016	Sridhar G. Iyengar et al., <i>Method and Apparatus for Assay of Electrochemical Properties</i> , U.S. Patent Application Publication No. 2005/0069892 (published Mar. 31, 2005) (“ Iyengar ”))
1017	Adam Heller et al., <i>Analyte Monitoring Devices and Methods of Use</i> , U.S. Patent No. 6,560,471 (issued May 6, 2003) (“ Heller-2003 ”))
1018	Leann M. Lesperance et al., <i>Calibration of the Continuous Glucose Monitoring System for Transient Glucose Monitoring</i> , Diabetes Technology & Therapeutics, Vol. 9, No. 2, pp. 183-190 (2007) (“ Lesperance ”))
1019	Eva Dock et al., <i>Multivariate Data Analysis of Dynamic Amperometric Biosensor Responses From Binary Analyte Mixtures—Application of Sensitivity Correction Algorithms</i> , 65 Talanta 298-305 (2005) (“ Dock ”))

Exhibit No.	Description of Exhibit
1020	David M. Fraser, <i>An Introduction to in vivo Biosensing: Progress and Problems</i> , in David M. Fraser, <i>Biosensors in the Body: Continuous In Vivo Monitoring</i> , Ch. 1, pp. 1-56 (John Wiley & Sons Ltd. 1997) (“ Fraser ”)
1021	Milena Koudelka-Hep, <i>Electrochemical Sensors for in vivo Glucose Sensing</i> , in David M. Fraser, <i>Biosensors in the Body: Continuous In Vivo Monitoring</i> , Ch. 2, pp. 57-77 (John Wiley & Sons Ltd. 1997) (“ Koudelka-Hep ”)
1022	Michael Schlosser and Manfred Ziegler, <i>Biocompatibility of Active Implantable Devices</i> , in David M. Fraser, <i>Biosensors in the Body: Continuous In Vivo Monitoring</i> , Ch. 5, pp. 139-170 (John Wiley & Sons Ltd. 1997) (“ Schlosser ”)
1023	George S. Wilson and Yanan Zhang, <i>Introduction to the Glucose Sensing Problem</i> , in David D. Cunningham and Julie A. Stenken, <i>In Vivo Glucose Sensing</i> , Ch. 1, pp. 1-27 (John Wiley & Sons, Inc. 2010) (“ Wilson ”)
1024	Marisha L. Godek and David W. Granger, <i>The Macrophage in Wound Healing Surrounding Implanted Devices</i> , in David D. Cunningham and Julie A. Stenken, <i>In Vivo Glucose Sensing</i> , Ch. 2, pp. 29-58 (John Wiley & Sons, Inc. 2010) (“ Godek ”)
1025	Timothy Henning, <i>Commercially Available Continuous Glucose Monitoring Systems</i> , in David D. Cunningham and Julie A. Stenken, <i>In Vivo Glucose Sensing</i> , Ch. 5, pp. 113-156 (John Wiley & Sons, Inc. 2010) (“ Henning ”)
1026	K. 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> , 21 Medical Progress through Technology 91-103 (1995) (“ Nishida ”)

Exhibit No.	Description of Exhibit
1027	Adam Heller, <i>Implanted Electrochemical Glucose Sensors for the Management of Diabetes</i> , 1 Annu. Rev. Biomed. Eng. 153 (1999) (“ Heller ”)
1028	S.J. Alcock and A.P.F. Turner, <i>Continuous Analyte Monitoring to Aid Clinical Practice</i> , 13 IEEE Engineering in Medicine and Biology 319-325 (1994) (“ Alcock ”)
1029	Megan C. Frost and Mark E. Meyerhoff, <i>Implantable Chemical Sensors For Real-Time Clinical Monitoring: Progress And Challenges</i> , 6 Current Opinion in Chemical Biology 633-641 (2002) (“ Frost ”)
1030	N. Wisniewski et al., <i>Characterization of Implantable Biosensor Membrane Biofouling</i> , 366 Fresenius J Analytical Chemistry 611-621 (2000) (“ Wisniewski ”)

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 Application No. 2005/0143636 to Zhang et al. (Exhibit 1004, “Zhang”) discloses and/or renders obvious the elements of claims 23-46 of U.S. Patent No. 11,020,031 B2 (“the ’031 patent”). I also have been asked to consider whether U.S. Patent Application No. 2005/0004439 to Shin et al. (Exhibit 1008, “Shin”) discloses and/or renders obvious the elements of claims 23-46 of the ’031 patent. I also have been asked to consider the state of the art at the time of the alleged invention claimed in the ’031 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 III, below.

3. I have been informed that DexCom, Inc. (“DexCom” or “Patent Owner”) purports to own the ’031 patent. To the best of my knowledge, I have no financial interest in DexCom or in the ’031 patent, and to the best of my knowledge, I have had no contact with DexCom or with the named inventors of the ’031 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 '031 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 '031 patent.

II. MATERIALS REVIEWED

5. In connection with my analysis and in reaching my opinions stated herein, I reviewed the '**031 patent (Exhibit 1001)**, including claims 23-46 of the patent in view of the specification, and I reviewed the prosecution history of the '031 patent (**Exhibit 1003**). I also reviewed the following documents:

- Zhang et al., *System and Method for Sensor Recalibration*, U.S. Patent Application Publication No. 2005/0143636 (published June 30, 2005) ("**Zhang**"), **Exhibit 1004**
- David A. Gough, *Method and Membrane Applicable to Implantable Sensor*, U.S. Patent No. 4,650,547 (issued Mar. 17, 1987), **Exhibit 1005**
- David A. Gough et al, *Complete Glucose Monitoring Systems with an Implantable, Telemetered Sensor Module*, U.S. Patent No. 4,703,756 (issued Nov. 3, 1987), **Exhibit 1006**
- Wayne A. Morgan et al., U.S. Patent Application Publication No. 2003/0076082, *Implantable Sensor Electrodes and Electronic Circuitry* (published Apr. 24, 2003) ("**Morgan**"), **Exhibit 1007**
- John J. Shin et al., *Real Time Self-Adjusting Calibration Algorithm*, U.S. Patent Application Publication No. 2005/0004439 (published Jan. 6, 2005) ("**Shin**"), **Exhibit 1008**

- John J. Mastrototaro et al., *Glucose Sensor*, U.S. Design Application No. 29/101,218 (U.S. Design Patent D433,755, issued Nov. 14, 2000) (the “**218 application**”), **Exhibit 1009**
- John J. Mastrototaro et al., *Glucose Monitor Calibration Methods*, U.S. Patent No. 6,424,847 (issued July 23, 2002) (“**Mastrototaro**”), **Exhibit 1010**
- James Say et al., *Analyte Monitoring Device and Methods of Use*, U.S. Patent No. 6,175,572 (issued Jan. 16, 2001) (“**Say**”), **Exhibit 1011**
- Benjamin J. Feldman et al., *A Method of Calibrating an Analyte-Measurement Device, and Associated Methods, Devices and Systems*, U.S. Patent Application Publication No. 2005/0239154 (published Oct. 27, 2005) (“**Feldman**”), **Exhibit 1012**
- William Peter Van Antwerp et al., *Hydrophilic, Swellable Coatings for Biosensors*, U.S. Patent No. 5,786,439 (issued July 28, 1998) (“**Van Antwerp**”), **Exhibit 1013**
- Marc D. Breton et al., *Method, System and Computer Program Product for Real-Time Detection of Sensitivity Decline in Analyte Sensors*, U.S. Patent Application Publication No. 2008/0172205 (published July 17, 2008) (“**Breton**”), **Exhibit 1014**
- John P. Willis, *Biofouling Self-Compensating Biosensor*, U.S. Patent Application Publication No. 2007/0299617 (published Dec. 27, 2007) (“**Willis**”), **Exhibit 1015**
- Sridhar G. Iyengar et al., *Method and Apparatus for Assay of Electrochemical Properties*, U.S. Patent Application Publication No. 2005/0069892 (published Mar. 31, 2005) (“**Iyengar**”), **Exhibit 1016**
- Adam Heller et al., *Analyte Monitoring Devices and Methods of Use*, U.S. Patent No. 6,560,471 (issued May 6, 2003) (“**Heller-2003**”), **Exhibit 1017**
- Lesperance et al., *Calibration of the Continuous Glucose Monitoring System for Transient Glucose Monitoring*, *Diabetes Technology & Therapeutics*, Vol. 9, No. 2, pp. 183-190 (2007) (“**Lesperance**”), **Exhibit 1018**

- Eva Dock et al., *Multivariate Data Analysis of Dynamic Amperometric Biosensor Responses From Binary Analyte Mixtures—Application of Sensitivity Correction Algorithms*, 65 *Talanta* 298-305 (2005) (“**Dock**”), **Exhibit 1019**
- David M. Fraser, *An Introduction to in vivo Biosensing: Progress and Problems*, in David M. Fraser, *Biosensors in the Body: Continuous In Vivo Monitoring*, Ch. 1, pp. 1-56 (John Wiley & Sons Ltd. 1997) (“**Fraser**”), **Exhibit 1020**
- Milena Koudelka-Hep, *Electrochemical Sensors for in vivo Glucose Sensing*, in David M. Fraser, *Biosensors in the Body: Continuous In Vivo Monitoring*, Ch. 2, pp. 57-77 (John Wiley & Sons Ltd. 1997) (“**Koudelka**”), **Exhibit 1021**
- Michael Schlosser & Manfred Ziegler, *Biocompatibility of Active Implantable Devices*, in David M. Fraser, *Biosensors in the Body: Continuous In Vivo Monitoring*, Ch. 5, pp. 139-170 (John Wiley & Sons Ltd. 1997) (“**Schlosser**”), **Exhibit 1022**
- George S. Wilson and Yanan Zhang, *Introduction to the Glucose Sensing Problem*, in David D. Cunningham and Julie A. Stenken, *In Vivo Glucose Sensing*, Ch. 1, pp. 1-27 (John Wiley & Sons, Inc. 2010) (“**Wilson**”), **Exhibit 1023**
- Marisha L. Godek and David W. Granger, *The Macrophage in Wound Healing Surrounding Implanted Devices*, in David D. Cunningham and Julie A. Stenken, *In Vivo Glucose Sensing*, Ch. 2, pp. 29-58 (John Wiley & Sons, Inc. 2010) (“**Godek**”), **Exhibit 1024**
- Timothy Henning, *Commercially Available Continuous Glucose Monitoring Systems*, in David D. Cunningham and Julie A. Stenken, *In Vivo Glucose Sensing*, Ch. 5, pp. 113-156 (John Wiley & Sons, Inc. 2010) (“**Henning**”), **Exhibit 1025**
- K. 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*, 21 *Medical Progress through Technology* 91-103 (1995) (“**Nishida**”), **Exhibit 1026**

- Adam Heller, *Implanted Electrochemical Glucose Sensors for the Management of Diabetes*, 1 Annu. Rev. Biomed. Eng. 153 (1999) (“**Heller**”), **Exhibit 1027**
- S.J. Alcock and A.P.F. Turner, *Continuous Analyte Monitoring to Aid Clinical Practice*, 13 IEEE Engineering in Medicine and Biology 319-325 (1994) (“**Alcock**”), **Exhibit 1028**
- Megan C. Frost and Mark E. Meyerhoff, *Implantable Chemical Sensors For Real-Time Clinical Monitoring: Progress And Challenges*, 6 Current Opinion in Chemical Biology 633-641 (2002) (“**Frost**”), **Exhibit 1029**
- N. Wisniewski et al., *Characterization of Implantable Biosensor Membrane Biofouling*, 366 Fresenius J Analytical Chemistry 611-621 (2000) (“**Wisniewski**”), **Exhibit 1030**

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.

20. I also have been informed that a prior art patent document (such as a an issued patent or a published patent application) may incorporate by reference another document, and that in such circumstances, the referenced document becomes effectively part of the patent document as if the referenced document were explicitly contained therein.

B. Obviousness

21. 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.

22. 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.

23. 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.

24. 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.

25. I have been informed that some documents published after the priority date may show the state of the art as it existed on the priority date.

26. 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

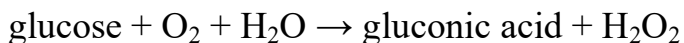
27. The '031 patent relates generally to continuous glucose monitoring systems and methods. Claims 23-46 of the '031 patent relate to systems and methods for monitoring glucose concentration in subcutaneous tissue, using a transcutaneous glucose sensor. Certain elements of the claims relate to sensor 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 November 7, 2008 (the earliest date to which the '031 patent claims priority).

A. Continuous Glucose Monitors (CGMs)

28. 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.*, Ex-1020 (Fraser) at 9.

29. Continuous glucose monitors, or CGMs, first became available commercially around the late 1990s as an alternative to the traditional fingerprick tests. Ex-1025 Chapter 5 (Henning) at 134. 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. Ex-1025 (Henning) at 135.

30. 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 (Ex-1020) at 58-59; Heller (Ex-1027) at 157-158; Wilson (Ex-1023) at 10.

31. The enzyme glucose oxidase must be immobilised to avoid enzyme loss. Enzyme immobilisation was (as of the priority date) and still is most often accomplished with the use of a membrane: the enzyme is contained within or behind a membrane and cannot diffuse freely from the membrane, and enzyme loss is thereby avoided.

32. For example, Koudelka-Hep explained in the late 1990s that, “[i]n the vast majority of sensors,” the enzyme glucose oxidase “is immobilised by glutaraldehyde cross-linking” to form “gel-like membranes.” Koudelka-Hep (Ex-1021) at 60 (discussing enzyme immobilisation techniques for electrochemical glucose sensors, in a section entitled “The Enzyme Membrane”); *see also* Koudelka-Hep (Ex-1020) at 59 (referring to the “enzymatic membrane”). The use of a membrane for immobilising the enzyme glucose oxidase remained

commonplace through the early 2000s. Henning, for example, when discussing CGMs commercially available around the 2009 timeframe, describes such sensors as presumptively containing an “enzyme-containing membrane.” Henning (Ex-1025) at 132 (referring to the “enzyme-containing membrane” for the “working electrode of the sensor [that] contains the enzyme glucose oxidase”). In a section entitled “5.4.2 The Signal,” which explains how commercial CGMs generate a signal in response to glucose level, Henning refers to the “enzyme membrane” as a component of commercial CGMs, without noting any exceptions:

An important consideration in the design of the electrode is the thickness of the enzyme membrane. The membrane needs to contain an excess of glucose oxidase so that all the glucose arriving at the membrane will be oxidized within the membrane. The amount of enzyme in the membrane will be determined by both the concentration of the enzyme in the membrane and the thickness of the membrane. The membrane controls the flux of glucose and oxygen into the membrane.

Henning (Ex-1025) at 133. Indeed, the very first CGMs employed a membrane to immobilise and stabilise glucose oxidase as well as control the diffusion of glucose. Henning (Ex-1025) at 120-122.

33. Membranes that coat the sensor serve additional purposes, including controlling the diffusion of glucose (as noted above) and improving biocompatibility. E.g., Fraser (Ex-1020) at 11-12 (discussing “mass transfer using

membranes”); Heller (Ex-1027) at 161 (“The glucose transport-limiting membrane is a key element in all implanted glucose-sensing devices.” (citations omitted)), 162-163 (“The biocompatible layer contacts the tissue in which the sensor or fiber is inserted. ... To avoid overgrowth in the 3-day period and also to avoid the adhesion of protein or platelets or the attachment of inflammatory response-related cells, the implant is coated with a nonfouled hydrogel, such as a hydrogel formed by cross-linking polyethylene oxide.” (citations omitted)); *see also* Willis (Ex-1015), ¶0026 (explaining that a membrane can provide “a biocompatible interface to body fluids and tissue” and can also prevent “migration of chemical species out of the biosensor, such as, for example, enzymes and mediators”); *see generally* Van Antwerp (Ex-1013) (describing biocompatible, hydrophilic coatings for biosensors and “methods for reducing the electrode impedance of implantable biosensors by coating the surface of the biosensor with a uniform hydrogel which allows unimpeded water movement around the sensor”).

B. Calibration and Drift

34. 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.

35. 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.*, Koudelka-Hep (Ex-1021) at 62-63.

36. 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.

37. 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.

38. 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).

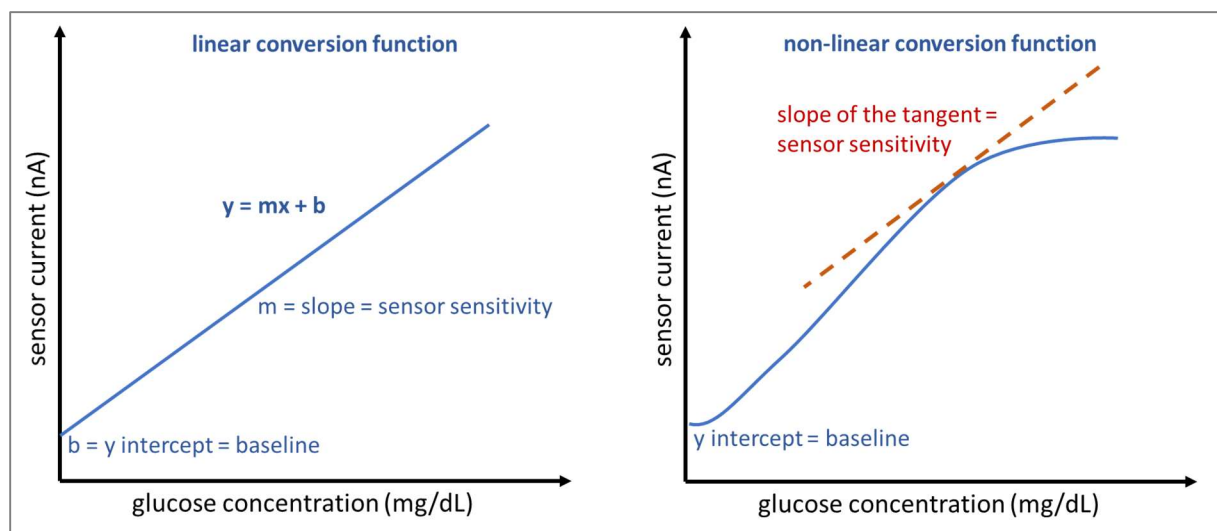
39. When the relationship between glucose concentration x and sensor output y is a linear relationship, the conversion function may be expressed by the equation $y = mx + b$, where:

- 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.

40. 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.

41. 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.



42. 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.

43. Many different factors, including factors related to sensor design and sensor materials, as well as factors concerning the in-vivo environment surrounding the sensor, affect sensor output with respect to glucose concentration. E.g., Koudelka-Hep (Ex-1021) at 64 (referring to “physiochemical interactions at the interface, material degradation, and local and systemic host response” as among the “different components of biocompatibility” that “determine the

longevity and performance of implanted sensors”); Schlosser (Ex-1022) at 142-143 (discussing the “two main variables which influence the biocompatibility of an implantable device: the material response and the host response”). Because some of these factors are not constant and are known to change during sensor wear, sensor sensitivity and baseline also can change during sensor wear. Changes in sensor sensitivity and/or baseline (and in the empirically-determined relationship between sensor output and glucose concentration) during sensor wear are often referred to as “drift.”

44. The occurrence of drift has been well documented in the art, for biosensors generally. E.g., Frost (Ex-1029) at 637 (referring to “sensitivities that continue to change with time” and “*in vivo* ‘drift’”); Dock (Ex-1019) at 299 (“Non-linearity of the response, baseline drift and loss of sensitivity with time are common problems with biosensors.”); Wisniewski (Ex-1030) at 611-612 (discussing sources of “declining sensor signal”); Nishida (Ex-1026) at 91 (explaining that “the output current of the glucose sensor decreases with time when *in vivo* subcutaneous tissue glucose monitoring is undertaken”); Wilson (Ex-1023) at 13 (referring to “sensor drift” and “signal drift adjustment”). Certain causes of drift also have been reported in the art. Both changes to the sensor’s materials (e.g., degradation of the sensor’s membrane(s)) and changes in the *in-vivo* environment

surrounding the sensor (e.g., the migration of cells towards the sensor) contribute to drift.

45. For example, Wisniewski discusses “two main categories” of sensor failure: “component-based failures,” which include membrane delamination, and “biocompatibility-based failures,” which include membrane biofouling, fibrous encapsulation, and membrane biodegradation. Wisniewski (Ex-1030) at 612; *see also* Wisniewski (Ex-1030) at 611 (Fig. 1).

46. Wilson discusses “four sources of failure or apparent failure of subcutaneously implanted glucose sensors.” These sources include changes to the sensor membrane as well as changes that occur in the in-vivo environment surrounding the sensor:

The first [source] is the passive loss of sensitivity resulting from uptake of species on or into the sensor. It is quite likely that these species are of relatively low molecular weight ... and could include protein fragments, lipids, and a variety of small endogenous molecules. This process is relatively rapid and has generally been referred to as the “run-in” time, lasting 2–4 h. In addition, a second necessary phase of the initial run-in time is the rehydration of sensor membranes that have been stored dry. It takes a finite amount of time for the membranes to hydrate and for the local microenvironment to establish the required mass transfer balance before stable operation can be achieved. The second [source] is the perturbation of oxygen and glucose levels in the tissue surrounding

the sensor resulting from tissue injury and the subsequent acute inflammatory response. This latter process, although complicated, has been studied in some detail and is described elsewhere in this book. It is typically manifested in sensor instability over the first 48 h but can result in cleanup of the small amount of capillary blood that may have accumulated. ... For long-term implants, two other issues can become important. There will be a loss of enzyme activity that will eventually affect sensor response. Finally, the capsule formation caused by the foreign body reaction may limit the access of glucose and oxygen to the sensor.

Wilson (Ex-1023) at 21-22.¹ *See also* Wilson (Ex-1023) at 17-18 (discussing sensitivity loss that occurs “in minutes” following implantation of subcutaneous sensors); Godek (Ex-1024) (describing the wound healing reaction to implanted

¹ The “run-in” period discussed in Cunningham, Chapter 1 is also discussed in Fraser, Chapter 2, where the author, around the late 1990s, discusses animal experiments of subcutaneous implanted glucose sensors and explains that an observation “common to most of these experiments was the so-called run-in period, i.e. the time after implantation necessary to obtain a stable current output,” and that “the duration of this period, during which the current decreases and then stabilises, varied from one hour ... to overnight.” Koudelka-Hep (Ex-1021) at 65-66 (citations omitted).

devices); Koudelka-Hep (Ex-1021) at 63-64 (referring to reports of “damaged sensor membranes” and including “material degradation” among the “components of biocompatibility” that will determine the “longevity and performance of implanted sensors”); Schlosser (Ex-1022) at 142-154 (discussing the host response, including the wound healing response, to implantable devices).

47. Frost similarly explains that “a substantial component of this *in vivo* ‘drift’ may well be related to the biological response of the host toward the foreign sensing device” (Frost (Ex-1029) at 637), such biological response including the “adsorption of proteins on the sensors surface,” which in turn can lead to the adherence of cells to the sensor (Frost at 633, 635 (Figure 2)). Such biological response is sometimes referred to as “biofouling” of the sensor. Frost (Ex-1029) at 638.

VI. OVERVIEW OF THE '031 PATENT

A. '031 Patent Specification

48. The '031 patent relates to “systems and methods for measuring an analyte in a host” (Ex-1001, 1:24-25), and notes that “continuous analyte sensors define a relationship between a sensor-generated signal and a reference measurement that is meaningful to a user (for example, blood glucose in mg/dL)” (Ex-1001, 143:3-6). “This defined relationship must be monitored to ensure that the continuous analyte sensor maintains a substantially accurate calibration,” and

“[u]nfortunately, both sensitivity *m* and baseline *b* changes can occur during in vivo sensor use, which requires calibration updates.” Ex-1001, 143:6-11. These changes may be caused by “blockage of sensor surface area due to cells and/or blood clotting at the membrane, blood flow/sheer rate, blood pH, temperature, hematocrit, [and] interfering drugs.” Ex-1001, 143:16-20.

49. The '031 patent describes methods that are stated to detect aberrant sensitivity changes, by using prior sensitivity information—e.g., sensitivity information obtained from prior in-vitro or in-vivo tests. Ex-1001, 140:12-135, 143:6-11, 213:9-13. The patent refers to a “profile” of expected changes in sensitivity over time:

In some circumstances, noise on the sensor signal can be mistaken as a drift in sensor sensitivity. It has been empirically determined, through evaluation of large in vivo and/or in vitro data sets, that sensor sensitivity generally follows an expected pattern of drift, over the period of sensor use. For example, in one exemplary sensor configuration, during the first hour or so, of sensor use (e.g., after start-up and/or re-start-up after a period of disuse), sensitivity tends to change rapidly; after this period, the sensitivity increase tends to level off and/or plateau. However other sensitivity *profiles* are possible based on sensor design. While each individual sensor's sensitivity *profile* can vary from that of other such sensors, depending upon factors such as sensor design, membrane chemistry, implantation site, and the like, it has been found that sensor *profiles* tend to follow an empirically

determined pattern of drift within a range of about $\pm 5\%$, $\pm 10\%$, $\pm 15\%$, $\pm 20\%$ or $\pm 25\%$. Deviations from the expected pattern can be indicative of noise on the sensor, sensor failure, and/or the like

Ex-1001, 210:40-58 (emphases added). Accordingly, a “profile” or “pattern of drift” can involve sensitivity changes where, “during the first hour or so, of sensor use (e.g., after start-up and/or re-start-up after a period of disuse), sensitivity tends to change rapidly; after this period, the sensitivity increase tends to level off and/or plateau,” and “other sensitivity profiles are possible based on sensor design.” Ex-1001, 210:44-50.

50. In addition, “an expected profile” can be “an expected pattern and/or amount of sensitivity change/drift over time,” such as where “sensor sensitivity tends to increase over time, wherein the increase tends to occur within an expected range.” Ex-1001, 213:14-19. The “expected profile” can be based on “a priori information,” as the patent describes in the following passage:

In general, a priori information includes information, data and/or observations generated during many previous in vitro and/or in vivo experiments, as well as information, data, and/or observations gleaned from the scientific literature. In some embodiments, the a priori sensitivity information includes and/or provides an expected profile (e.g., an expected pattern and/or amount of sensitivity change/drift over time). For example, it has been observed that in some sensor designs, the sensor sensitivity tends to increase over time, wherein the increase

tends to occur within an expected range. For example, it has been observed that sensor sensitivity tends to increase over time (e.g., no substantial decrease over time), wherein the increase tends to occur within an expected range, wherein the magnitude of the change is related to the length of time the sensor has been used and/or implanted and/or energized (e.g., turned on). Deviation from the expected profile can be indicative of a failure of a portion of the integrated system, a detrimental change in the host's condition, and/or the like, in some embodiments. In some embodiments, the system is configured to evaluate and/or consider a deviation from the expected profile in combination with additional information (e.g., interferents, noise, completion of break-in, etc.) to determine if a system failure has occurred.

Ex-1001, 213:9-32.

51. Regarding “an expected range” of sensitivity change over time, the patent describes embodiments where “the a priori sensitivity information defines a range (e.g., within boundaries and/or guard bands) of acceptable change (increase and/or decrease) in sensitivity,” such “an acceptable change in sensitivity” being “related to how long the sensor has been in use, implanted and/or energized.” Ex-1001, 213:33-36. “For example, in some circumstances, sensitivity can change (e.g., drift) up to about $\pm 5\%$, $\pm 10\%$, $\pm 15\%$, $\pm 20\%$, $\pm 25\%$, $\pm 30\%$, $\pm 40\%$, $\pm 50\%$, $\pm 60\%$, $\pm 70\%$, $\pm 80\%$, $\pm 90\%$, $\pm 100\%$, $\pm 200\%$ or more over a given time period” Ex-1001, 213: 36-41.

52. The patent further describes embodiments where “a change in sensitivity is evaluated using a ‘cone’ of feasible sensitivity values of the sensor.”

Ex-1001, 213:44-45.

In some embodiments, a change in sensitivity is evaluated using a “cone” of feasible sensitivity values of the sensor, such that aberrant sensitivity changes (e.g., artifacts) are detected whenever the sensitivity value (e.g., amount of sensitivity change, a calculated change in sensitivity over a time period) falls (e.g., occurs) outside of the cone of possibility. In one embodiment, the cone of possible sensitivity values is defined in terms of a range of allowable (or feasible) sensitivity change for a time point during a sensor session. The range of allowable sensitivity change can change over time during a sensor session, for example, by allowing a greater sensitivity change during an earlier time period of a sensor session than a later time period of a sensor session. In general, sensitivity information depends upon sensor design and can be obtained from analysis of data sets (e.g., a priori information). A known feasible range can be represented (e.g., drawn) on a graph as a “cone of possible sensitivity values” (e.g., a range of possible calculated sensitivity values, for the next time period, based at least in part on one or more previously calculated sensitivity value(s) and a priori information). In some embodiments, one or more criteria used to determine the cone of possible sensitivity values are defined by an expected profile.

Ex-1001, 213: 44-66.

B. Priority Date

53. The '031 patent claims priority to an application filed on November 7, 2008. Ex-1003 at 1-442. I have been instructed by counsel to apply November 7, 2008 as the priority date and date of the claimed invention for the purposes of my analysis.

C. Claims 23-46

54. Claims 23-46 of the '031 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 related to drift. Claims 23, 35, and 42 are independent claims, and claims 24-34, 36-41, and 43-46 are dependent claims.

55. Independent claims 23, 35, and 42 alternatively recite the information element as follows:

- “information associated with a drift profile, wherein the drift profile is associated with a shift over time in measurement characteristic of the transcutaneous glucose sensor to the glucose concentration within the body of the host resulting from the in vivo portion of the transcutaneous glucose sensor being within the body of the host for a period of time” (claim 23);

- “information associated with an expected change over time in a relationship between the signal and the glucose concentration within the body of the host” (claim 35);
- “a priori information, wherein the a priori information comprises an expected relationship between the signal and a glucose concentration existing within the body of the host, wherein the relationship changes as a function of time” (claim 42).

56. Claim 23 recites a “measurement characteristic of the transcutaneous glucose sensor to the glucose concentration,” while each of claims 35 and 42 recites a change over time in a “relationship between the signal” and the “glucose concentration.” These relationships are described by the conversion function, which defines calibration parameters such as sensitivity and baseline. In addition, all three claims require a shift or change over time, in the measurement characteristic (claim 23) or in the relationship (claims 35 and 42), and thus encompass shifts or changes over time in sensor sensitivity and/or in baseline. Claims 35 and 42 further refer to “an expected” change or relationship.

57. Notwithstanding the different recitations in the independent claims, these claims encompass the same embodiments that are disclosed in the prior art, as detailed below.

D. Prosecution History

58. The '031 patent was filed as U.S. Patent Application No. 17/132,664 on December 23, 2020. Ex-1003 at 1-442. The patent claims priority to an application filed on November 7, 2008. For this declaration, I have been asked to assume that the priority date of the '031 patent is November 7, 2008.

59. The application for the '031 patent was filed with 18 claims, along with a “Track One” request for prioritized examination. Ex-1003 at 1, 425-426.

60. On December 20, 2020, about one week after filing the application, the applicant canceled claims 1-18 and added claims 19 and 20, which are shown below (*see* Ex-1003 at 443-448):

AMENDMENTS TO THE CLAIMS

1-18. (Cancelled)

19. (New) A method comprising:
calibrating sensor data.

20. (New) A transcutaneous analyte sensor system comprising:
a transcutaneous analyte sensor; and
sensor electronics operably connectable to the transcutaneous analyte sensor.

61. On January 4, 2021, the applicant filed an information disclosure statement (“IDS”) that listed a number of documents and spanned 166 pages. Ex-1003 at 449-618.

62. In a Non-Final Office Action dated March 2, 2021, the Examiner rejected claims 19 and 20 (shown above) for being anticipated by the prior art. Ex-1003 at 634-639. The Examiner also electronically initialed the pages of the IDS. Ex-1003 at 759-924.

63. On March 15, 2021, the applicant filed a Response, in which the applicant cancelled claim 19, significantly amended claim 20 (which issued as claim 1), and added over 40 new claims. Ex-1003 at 926-937. The amendments to claim 20 are shown below:

AMENDMENTS TO THE CLAIMS

Please cancel claim 19 without prejudice.

Please amend claim 20 and add claims 21-65 as follows.

1-18. (Canceled)

19. (Canceled)

20. (Currently Amended) A ~~transcutaneous analyte sensor~~ system for monitoring a glucose concentration, the system comprising:

a transcutaneous ~~analyte~~ glucose sensor comprising:

an *ex vivo* portion configured to remain outside of a body of a host; and

an *in vivo* portion configured to be inserted into the body of the host, wherein the *in vivo* portion comprises:

an electrode; and

a membrane disposed over at least a portion of the electrode, wherein the membrane comprises at least one enzyme;

wherein the transcutaneous glucose sensor is configured to generate a signal, wherein the magnitude of the signal depends upon a glucose concentration existing at the *in vivo* portion of the transcutaneous glucose sensor inserted into the body of the host; and

sensor electronics configured to operably ~~connectable~~ connect to the transcutaneous ~~analyte~~ glucose sensor, wherein the electronics comprises a memory, wherein the memory stores information associated with a profile, wherein the profile is based at least in part on *a priori* information related to expected sensitivity changes associated with a length of time the *in vivo* portion of the transcutaneous glucose sensor has been inserted into the body of the host.

64. On March 16, 2021 (which is one day after applicant's amendments to the claims), the applicant and the Examiner conducted an interview. The Interview

Summary states that the Examiner “agreed that the claim amendments filed on March 15, 2021 were patentable in light of the prior art.” Ex-1003 at 953.

65. A Notice of Allowance was mailed on March 26, 2021. Ex-1003 at 989-1002. The '031 patent issued on June 1, 2021. Ex-1003 at 1058; Ex-1001.

VII. LEVEL OF ORDINARY SKILL IN THE ART

66. 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 November 7, 2008 is the priority date for purposes of this declaration.

67. 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.

68. 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

69. I have been informed that, in the co-pending district court litigation, Petitioner has proposed that the term “drift profile” recited in claims 23, 25-28, and 34 means “profile of a change in baseline and/or sensitivity of the sensor signal over time,” and that Patent Owner has asserted that the term be given its plain and ordinary meaning, which, according to Patent Owner, is a “set of information associated with sensor measurement characteristic changes over time.” My analysis and conclusions set forth below are the same under either construction. In other words, the embodiments of Zhang and of Shin discussed below disclose a “drift profile,” regardless of whether the term “drift profile” is construed as proposed by Petitioner or as proposed by Patent Owner.

70. For the purpose of this declaration, I have been asked to assume that each of the other claim terms 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 meanings of the claim terms in my analysis.

IX. OVERVIEW OF THE PRIOR ART

A. Zhang (Ex-1004)

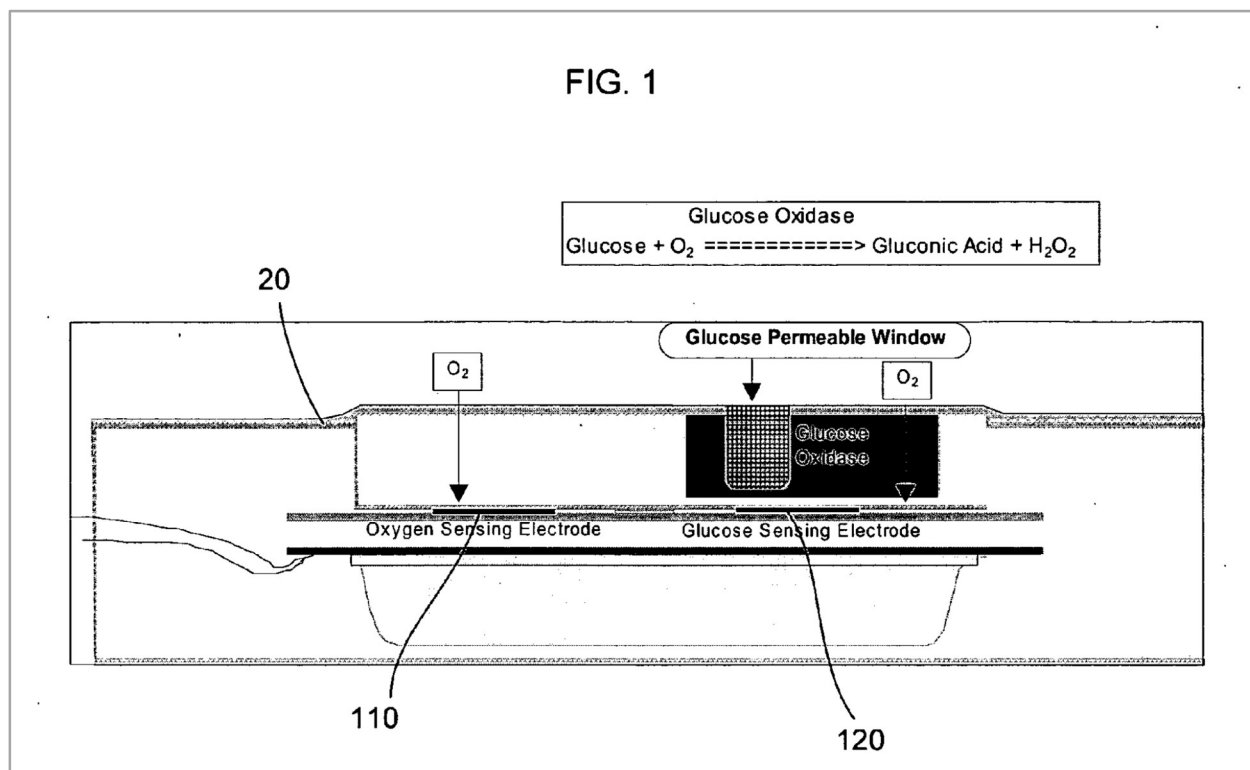
71. U.S. Patent Application Publication No. 2005/0143636, entitled *System and Method for Sensor Recalibration*, was published on June 20, 2005, and is referred to herein as “Zhang.” During prosecution of the ’031 patent, the applicant did not include Zhang in the references listed in the IDS. Ex-1003 at 449-614 (pages of IDS listing U.S. patent application publications).

1. Transcutaneous glucose sensor and sensing system

72. Zhang describes calibration methods for implantable sensors that measure a characteristic of a patient’s body, which in preferred embodiments is glucose level. Ex-1004, ¶0027. The sensor may be part of “an implantable sensing system” that includes “a processor” and other components. Ex-1004, ¶0013. “The sensor may be a glucose sensor.” Ex-1004, ¶0014.

73. The sensor can include an enzyme electrode that is used “for direct contact with patient fluids.” Ex-1004, ¶0028. Zhang describes sensor electrodes using the enzyme glucose oxidase to generate currents, such that “a measurement of the currents can be used to determine the amount of glucose present in the blood.” Ex-1004, ¶0029; *see also* Ex-1004, ¶0030.

74. FIG. 1 of Zhang “shows a cross-sectional view of an exemplary sensor according to an embodiment of the present invention” (Ex-1004, ¶0020) and is reproduced below:



75. In such embodiments, “a glucose oxygen sensor 20” measures the depletion of oxygen as the enzyme glucose oxidase catalyzes the reaction between glucose and oxygen. Ex-1004, ¶0028.

76. Zhang incorporates by reference several other patent documents, including U.S. Patent Nos. 4,650,547 (Ex-1005) and 4,703,756 (Ex-1006), and U.S. Patent Application Publication No. 2003/0076082 (“Morgan,” Ex-1007). These documents relate to glucose monitoring systems.

2. Calibration

77. Zhang explains that “[s]ensors typically exhibit different characteristics during the useful life of the sensor” and “typically have three phases: (1) initialization phase, (2) stable phase, and (3) end of life phase.” Ex-1004, ¶0032. Zhang teaches that the readings from the sensor need to be adjusted, to account for the different sensor characteristics in each of these three phases. Zhang describes “a calibration scheme” that “can be used to properly calibrate the sensor regardless of the phase of the sensor life and to identify which phase the sensor is in.” Ex-1004, ¶0032. Zhang’s calibration scheme “adjusts the calibration curve throughout the life of the sensor. Having a constantly updated calibration curve assures that accurate sensor readings are obtained regardless of the phase of the sensor.” Ex-1004, ¶0040.

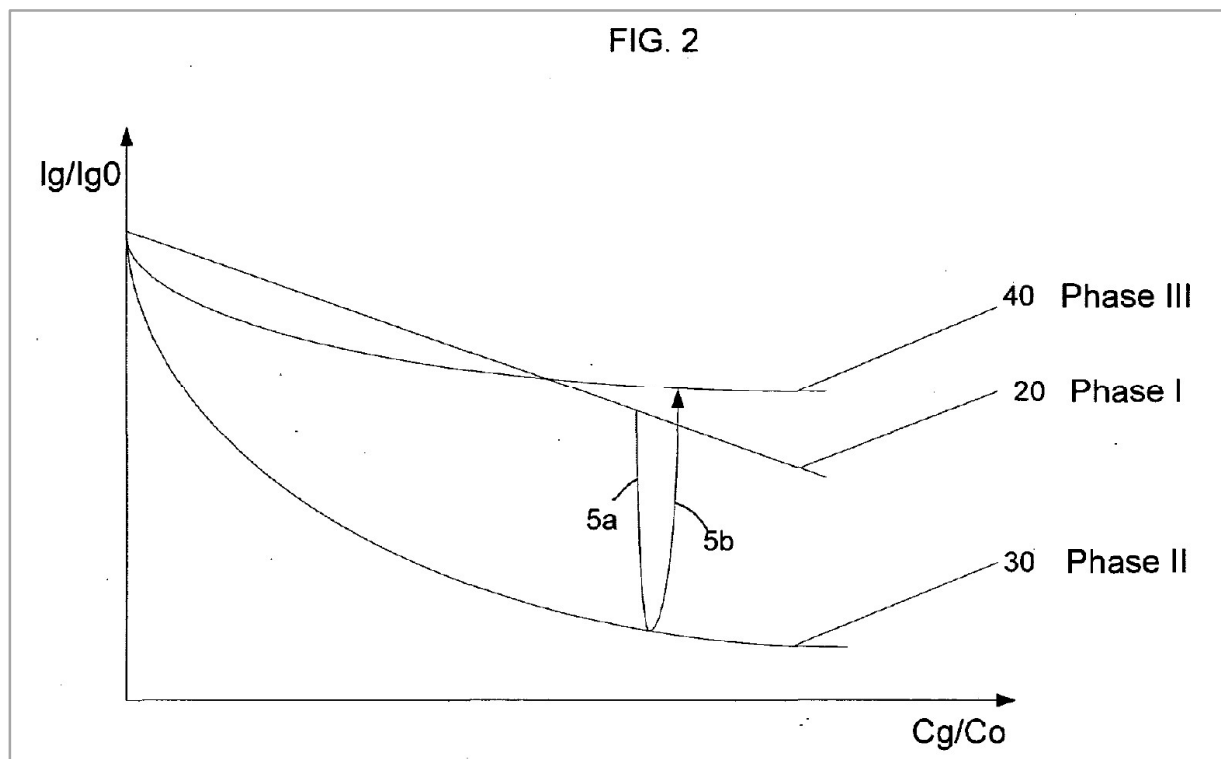
78. In Zhang’s calibration method, the calibration curve undergoes “curve shape adjustments” so that the shape of the calibration curve appropriately reflects the particular phase of sensor life that applies at that point in time. Ex-1004, ¶¶0051-0061, FIG. 4. “[A]djustments may be made to the shape of the measured curve, i.e., the shape of the sensor calibration curve. The adjustments to the calibration curve may be used to provide calculation of the sensor output.” Ex-1004, ¶0051. Zhang uses expected curve shapes (generated from empirical data collected from prior use of sensors) to adjust the shape of the measured curve

during sensor use; Zhang refers to the expected curve shapes as “the expected normalized calibration curves.” Ex-1004, ¶0033; *see also* Ex-1004, ¶0021.²

79. Zhang teaches how to adjust the shape of the calibration curve in ¶¶0033-0061 and by reference to FIG. 2. FIG. 2 shows three normalized curve shapes, each curve shape corresponding to one of the three phases of sensor life. Zhang explains that each curve reflects “a sensitivity period” and characterizes the varying relationships between sensor current and glucose concentration over time periods following sensor insertion. Ex-1004, ¶¶0033-0040. The curves in FIG. 2 show how “sensor output current with respect to glucose concentration” (and thus sensor sensitivity³) changes in each phase of sensor life, and each curve in FIG. 2 shows sensor sensitivities for a particular phase of sensor life. FIG. 2 is reproduced below:

² Zhang also describes shifting sensor data based on blood glucose concentration measured by a blood glucose meter. Ex-1004, ¶0044 (“According to embodiments of the present invention, the nominal glucose current (I_{g0}) may be adjusted by calculating a shift of each measured data point with respect to the blood glucose meter readings.”).

³ *See* ¶¶38-42.



80. Zhang explains that “[t]he curve shapes 20, 30, and 40 are the calibration curve shapes of each phase of the sensor life,” and that “[a]rrow 5a, 5b represent a typical life cycle of the calibration curves as the sensor changes from one phase to another phase.” Ex-1004, ¶0033. During sensor wear, reference blood glucose values are obtained,⁴ and, in combination with prior knowledge of the phases and associated normalized calibration curves, the system is recalibrated.

⁴ Recalibration involves using “independent glucose readings, such as readings from a blood glucose meter taken simultaneously during the life of the sensor.” Ex-1004, ¶0041.

Ex-1004, ¶0040. Updating the calibration curve by this method contributes to more accurate sensor readings. Specifically, as a sensor progresses through the three phases, its output with respect to glucose concentration (and thus its sensitivity) first will be described by the shape of curve 20, then by the shape of curve 30 (arrow 5a showing the shift from curve 20 to curve 30), and then by the shape of curve 40 (arrow 5b showing the shift from curve 30 to curve 40). Zhang thus teaches a profile, based on the shift between three curve shapes over time, that is used to update the calibration curve. The updated calibration curve is then used to generate sensor readings, i.e., calibrate sensor data. Ex-1004, ¶¶0041-62; *see also* Ex-1004, ¶0033 (“...sensor recalibrations will be performed not only based on independent characteristic values (e.g., blood meter values) but with use of the expected normalized calibration curves...”). Zhang refers to a “curve shape adjustment” in FIGS. 4 and 5c.

81. The normalized curve shapes depicted in FIG. 2 are “the calibration curve shapes of each phase of the sensor life as determined based on empirical data collected from the use of sensors.” Ex-1004, ¶0033. In other words, the shape of each curve in FIG. 2 was determined based on a priori information. *See also* Zhang, ¶¶0015-0017; Ex-1004, ¶0016 (“Generating a calibration curve may include compiling a priori empirical values of sensors similar to the sensor being calibrated.”).

82. Zhang recognizes that a calibration scheme that adjusts the calibration curve during sensor wear would be useful for “most sensors”: “Although the normalized calibration curves in FIG. 2 were originally derived based on glucose sensors, further research has proved that most sensors behave similarly and these calibration curves can be used with other type of sensors.” Ex-1004, ¶0033.

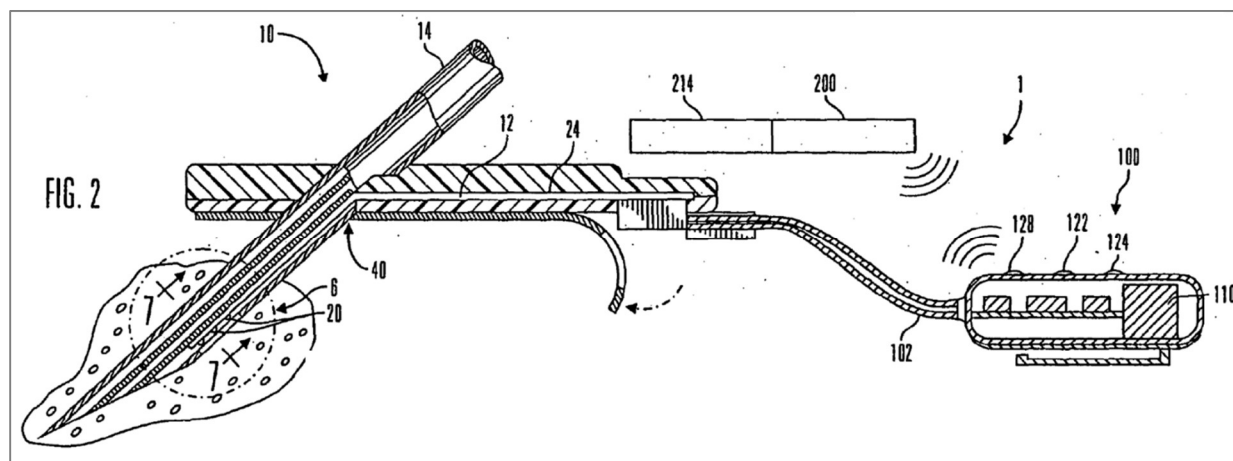
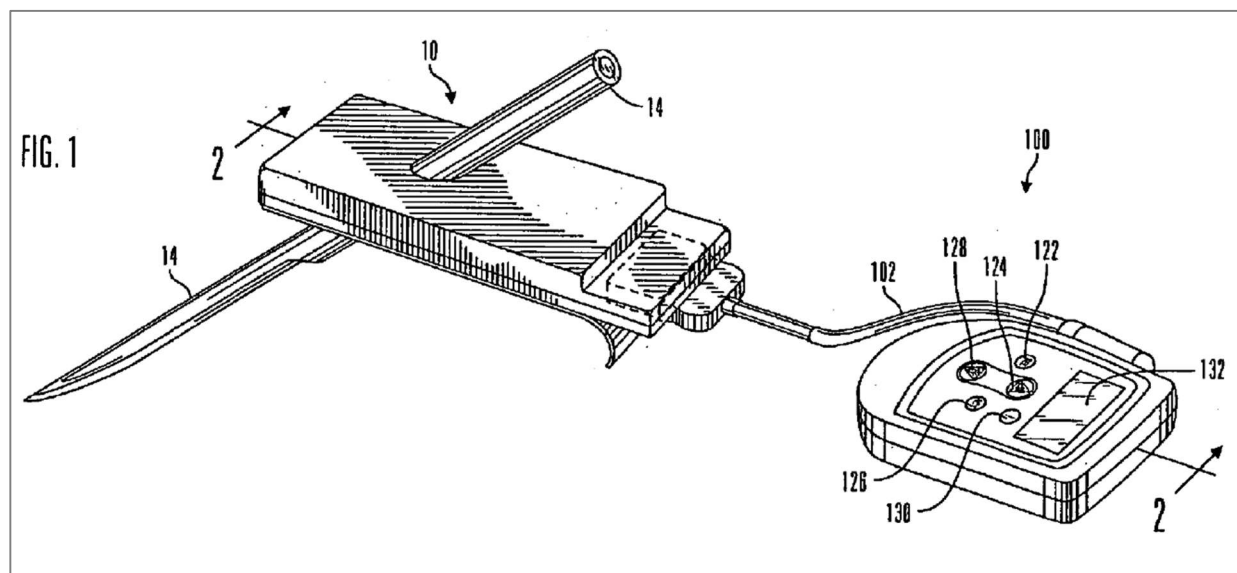
B. Shin (Ex-1008)

83. U.S. Patent Application Publication No. 2005/0004439, entitled *Real Time Self-Adjusting Calibration Algorithm*, was published on January 6, 2005, and is referred to herein as “Shin.” During prosecution of the ’031 patent, the applicant listed Shin in an IDS. Ex-1003 at 520. The Examiner did not cite Shin in any rejection of claims. Ex-1003 at 640.

1. Transcutaneous glucose monitoring device

84. Shin describes “calibration methods for a glucose monitor that is coupled to a sensor set to provide continuous data recording of readings of glucose levels from a sensor for a period of time.” Ex-1008, ¶0064. Shin’s system includes multiple components: “the glucose monitor 100, which attaches to the glucose sensor set 10; and the data processor 200.” Ex-1008, ¶0059.

85. FIG. 1 and FIG. 2 from Shin are reproduced below. FIG. 1 shows the “sensor set 10,” and FIG. 2 shows the “sensor set 10” and the “data processor 200”:



86. As shown in FIG. 2 above, the electrochemical sensor 12 “extends from the glucose sensor set 10 into the user’s body with electrodes 20 of the glucose sensor 12 terminating in the user’s subcutaneous tissue.” Ex-1008, ¶0057.

87. Shin incorporates by reference several documents, including Application No. 29/101,218, entitled “Glucose Sensor” (Ex-1009).

2. Calibration

88. Shin teaches “[a] method of calibrating glucose monitor data include[ing] collecting the glucose monitor data over a period of time at predetermined intervals [and] calculation of the calibration characteristics.” Ex-1008, Abstract; Shin, ¶¶0005-0028, ¶¶0054-0182 (generally teaching analyte sensors and methods for calibrating the sensors).

89. Shin teaches that a “calibration factor called a sensitivity ratio (SR) ... is calculated for a particular glucose sensor 12. The SR [the sensitivity ratio or blood glucose level/Valid ISIG value] is a calibration factor used to convert the Valid ISIG value [electrical current signal] (Nano-Amps) into a blood glucose level (mg/dl or mmol/l).” Ex-1008, ¶ 0082. Further, under the assumption that the Valid ISIG will be 0 when the blood glucose is 0, Shin utilizes a “single-point calibration equation” to calculate a single-point sensitivity ratio (“SPSR”). Ex-1008, ¶¶ 0088-0089. The calibrated blood glucose level is then “Blood Glucose Level – Valid ISIG*SPSR.” Ex-1008, ¶ 0090. Alternatively, Shin teaches using a modified SPSR (“MSPSR”) as a calibration factor; the MSPSR accounts for a

sensor “hav[ing] a less linear performance at very high blood glucose levels.” Ex-1008, ¶0093.⁵

90. Shin teaches comparing the MSPSR to valid sensitivity ranges. Specifically, Shin teaches that, during calibration, “the MSPSR is compared to a valid sensitivity range to determine if the newly calculated MSPSR is reasonable.” Ex-1008, ¶0103. Shin describes a particular embodiment using “a valid MSPSR range of 1.5 to 15” that “has been determined based upon valid glucose sensor sensitivity measurements made in-vitro.” Shin also teaches that “[o]ther valid sensitivity ranges may be applied depending on the types of sensors to be calibrated, the range of acceptable sensitivity levels for the various sensor types, the manufacturing consistency expected for the sensors, environmental conditions, how long the sensor has been in use, or the like.” Ex-1008, ¶0103.

91. Shin thus teaches checking for changes in sensor sensitivity using a priori information. In particular, Shin teaches comparing the calibration factor (the

⁵ Shin teaches that the relationship between sensor output and glucose concentration is a linear relationship. Ex-1008, ¶¶0087-0102. In Shin, the SPSR (or MSPSR, as the case may be) is the inverse of the slope m and thus is the inverse of sensor sensitivity.

MSPSR) to pre-determined “valid sensitivity ranges” that can be based on “how long the sensor has been in use.” Ex-1008, ¶0103.

X. THE CLAIMS IN VIEW OF THE PRIOR ART

A. Zhang Anticipates and/or Renders Obvious Claims 23-46 of the '031 Patent

92. Claims 23-46 of the '031 patent are anticipated by Zhang (Ex-1004), and/or are rendered obvious by Zhang in view of the POSA's knowledge. An overview of Zhang is provided above. My specific analysis of Zhang for every element of claims 23-46 is provided below.

1. Independent Claim 23

a) 23[Pre]. “A method for monitoring a glucose concentration, the method comprising:”

93. To the extent the preamble is limiting, Zhang discloses it. Zhang describes a method for monitoring glucose concentration. Ex-1004, ¶0007 (describing a “method for calibrating a sensor”), ¶0008 (referring to “glucose electrode readings”), ¶0014 (“The sensor may be a glucose sensor.”), ¶0027 (“Embodiments of the present invention are directed to calibration techniques for use with implantable sensors that measure a characteristic of a patient's body. In preferred embodiments, the characteristic is the glucose level....”).

- b) **23[a]. “beginning a sensor session associated with use of a transcutaneous glucose sensor, wherein the transcutaneous glucose sensor comprises: an ex vivo portion configured to remain outside of a body of a host; and an in vivo portion configured to be inserted within the body of the host;”**

94. Zhang discloses the element of claim 23[a], and in the alternative renders claim element 23[a] obvious.

95. Zhang discloses beginning a sensor session. Zhang describes methods for calibrating glucose sensor data, where the sensor readings are processed as described therein. Ex-1004, ¶¶0037-0063. By teaching obtaining and then processing sensor output, Zhang teaches beginning a sensor session. *See also* Ex-1004, ¶0013 (referring to “an output of the sensor”), ¶¶0041-0062 (describing adjustments to sensor readings).

96. Zhang’s sensor session is associated with the use of a transcutaneous glucose sensor comprising an ex-vivo portion configured to remain outside the body and an in-vivo portion configured to be inserted into the body. Zhang explains that the sensor “can be implanted in and/or through subcutaneous, dermal, sub-dermal, inter-peritoneal or peritoneal tissue,” and that “the implantable sensor may be used in ... interstitial fluid....” Ex-1004, ¶0027. Specifically, Zhang explains that

embodiments of the present invention are not limited to implantation in an artery or vein, but can be *implanted in and/or through*

subcutaneous, dermal, sub-dermal, inter-peritoneal or peritoneal tissue. ... The implantable sensor is primarily adapted for use with blood. However, still further embodiments of the implantable sensor may be used in other bodily fluids, such as *interstitial fluid*, spinal fluid, saliva, urine, tears, sweat, or the like.

Ex-1004, ¶0027 (emphases added).

97. Sensors having an ex-vivo portion also would have been obvious in view of the POSA's knowledge that many glucose sensors described in the art—including sensors used commercially—were transcutaneous sensors having an ex-vivo portion. Indeed, a transcutaneous sensor having an ex-vivo portion was a common feature of commercial CGMs. E.g., Henning (Ex-1025) at 131-132 (“All the on-market CGM devices have similar components The sensor has a glucose-oxidase-based working electrode located under the skin and electrical contacts located above the skin.”), 143 (Figure 5.18). The POSA would have recognized that systems with such sensors offer advantages over systems with fully implanted sensors; for example, systems with a transcutaneous sensor as claimed can be “worn continuously by changing the systems every 3-7 days” and “are inserted by the user at home” and thereby “allow a user to choose how often and at what times they want to wear the device.” Henning (Ex-1025) at 129. Systems with transcutaneous sensors provide flexibility, in contrast to long-term systems with sensors that are “implanted in the body,” which “require a long-term commitment

to the use of the device” and where “[i]nserting the long-term device and retrieving it from the body” would “likely be done in a physician’s office.” Henning (Ex-1025) at 129. The POSA would have reasonably expected success in using a transcutaneous sensor as claimed given the successful use of such sensors in the art.

98. Moreover, Zhang teaches that its calibration scheme is a “generalized method [that] may be applied to a variety of glucose sensors.” Ex-1004, ¶0031. *See also* Ex-1004, ¶0033 (“[F]urther research has proved that most sensors behave similarly and these calibration curves can be used with other type of sensors.”).

c) 23[b]. “generating sensor data derived at least in part from the transcutaneous glucose sensor;”

99. Zhang discloses the element of claim 23[b].

100. Zhang’s method involves generating sensor data at least in part from the sensor. The electrodes of the sensor, which are implanted in the user, generate current, and this current is measured to generate sensor data. Ex-1004, ¶0029 (“a measurement of the currents can be used to determine the amount of glucose present in the blood”), ¶¶0042-0062 (referring to “glucose electrode readings” and “nominal glucose current”).

- d) 23[c]. “determining a glucose concentration value based at least in part on the sensor data and information associated with a drift profile, wherein the drift profile is associated with a shift over time in measurement [sic] characteristic of the transcutaneous glucose sensor to the glucose concentration within the body of the host resulting from the in vivo portion of the transcutaneous glucose sensor being within the body of the host for a period of time;”**

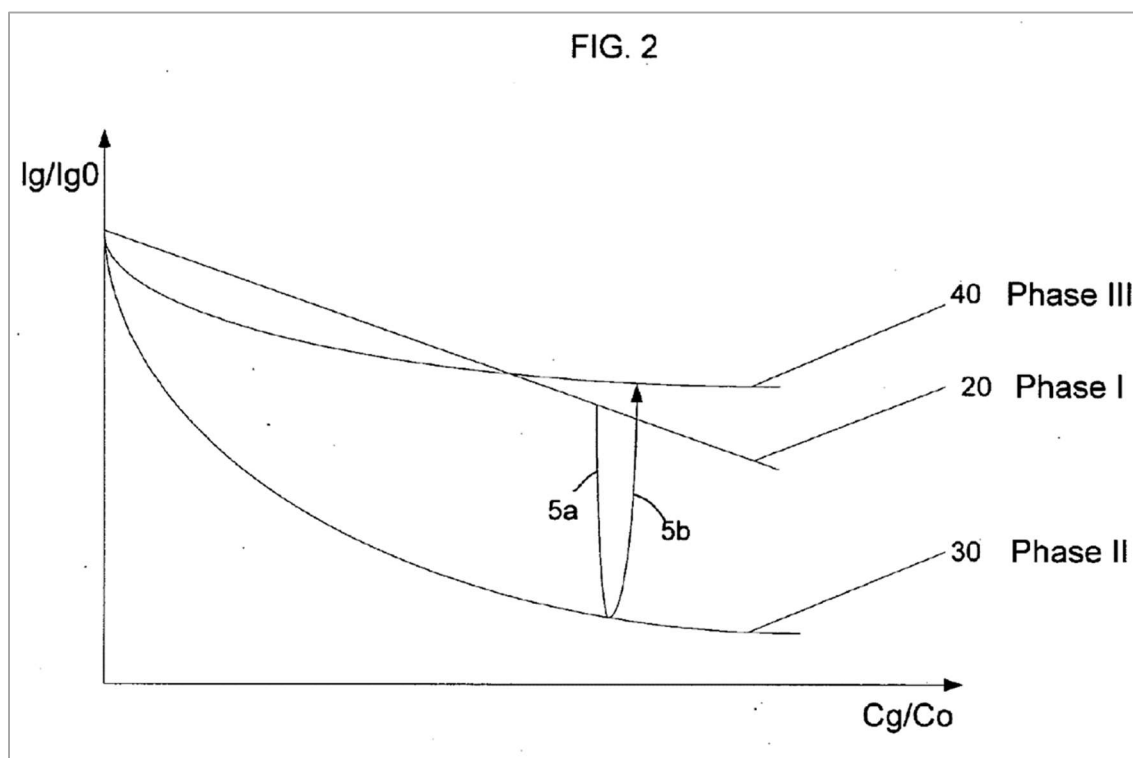
101. Zhang discloses the element of claim 23[c].

102. Zhang’s method involves determining a glucose concentration value based at least in part on the sensor data and on pre-determined, normalized calibration curves for each of the three phases of sensor life, as described below. Zhang’s normalized calibration curves and shifts between curves constitute a “drift profile,” wherein the “drift profile” is associated with “a shift over time” in sensitivity (a “measurement characteristic” of the sensor to the glucose concentration) resulting from the sensor being within the body of the host for a period of time. Thus Zhang’s method involves “determining a glucose concentration value based at least in part on the sensor data and information associated with a drift profile,” as recited in claim 23[c].

103. Zhang teaches calibrating the sensor output and determining a glucose concentration value, using normalized calibration curves. Ex-1004, ¶¶0031-0063. The curves reflect a shift over time of sensor output with respect to glucose concentration, as the sensor progresses through the three phases of sensor life.

Zhang, ¶¶0033-0040. This shift over time is a result of the length of time the sensor has been inserted in the host and reflects a shift in sensor sensitivity (a “measurement characteristic” as claimed) over time. Ex-1004, ¶¶0033-0040. Thus Zhang’s three curves and the shifts between them over time constitute a “drift profile” as recited in claim 23[c].

104. Zhang depicts an embodiment of normalized calibration curves in FIG. 2; FIG. 2 shows three curves “for the three phases of the sensor life” (Ex-1004, ¶0033) and is reproduced below:



105. As Zhang explains in ¶¶0037-0039, each of the curves in FIG. 2 has a different shape, the different shapes showing that each phase of sensor life is

associated with different sensor sensitivities. In other words, each curve reflects sensor sensitivities for a particular phase of sensor life.

106. Zhang's three curves have slopes that differ from each other and thus the curves exhibit different sensor sensitivities for the different phases of sensor life. For the linear relationship between sensor output and glucose concentration shown as "line 20" for Zhang's phase I, the relationship is expressed by the equation $y = mx + b$, where the slope m is the sensor sensitivity. For the non-linear relationships shown by curve 30 and curve 40 (for Zhang's phase II and phase III, respectively), the slope or sensitivity of the sensor at a given concentration is the slope of the tangent on the curve at that concentration. See ¶¶38-41, above. By examining FIG. 2, it can be seen that the slope of line 20 is different from at least some slopes of tangents of curves 30 and 40, and that Zhang's three curves have slopes that differ from each other and thus the curves exhibit different sensor sensitivities.

107. Zhang then describes "a continuum of change" in sensor sensitivity; as time moves forward and the sensor progresses through the different phases, sensitivity follows the shape of the three normalized curves, and the calibration curve is adjusted to account for each shift in curve shape (each shift being a change in sensor sensitivity):

[P]hase 1 of the sensor's life may be viewed as a sensitivity period during the initial output of the sensor current with respect to glucose concentration. As can be seen in FIG. 2, line 20 is virtually completely linear during the first phase. This linearity represents the sensor output when it is initially placed in a patient. However, as the sensor stabilizes and enters phase 2, the current output of the sensor with respect to glucose concentration tends to become non-linear. The curve shape moves from line 20 to curve 30, as shown by the arrow 5a. ... The curve shift between line 20 and curve 30, represented by arrow 5a, represent[s] a continuum of change in the sensor output current with respect to glucose concentration[.]...Toward the end of the sensor life, the sensor output current tends to change less and less with respect to glucose concentration. Curve 30 moves toward curve 40 as represented by arrow 5b.

Ex-1004, ¶¶0037-0039; ¶0040 (“the present invention adjusts the calibration curve throughout the life of the sensor”), ¶0051, ¶¶0061-0062.

108. The three curves in FIG. 2 and the shifts between them as time progresses are a “drift profile” as recited in claim 23[c] because they reflect the shift in sensor sensitivity that occurs over time (i.e., as a result of the sensor being within the body of the host). *See also* Zhang's claims 34-37.

109. Furthermore, Zhang teaches that “sensor recalibrations will be performed not only based on independent characteristic values (e.g., blood meter

values) but with use of the expected normalized calibration curves.” Ex-1004, ¶0033. The sensor recalibrations are used in determining a glucose concentration. Ex-1004, ¶0029, ¶0033-0035, ¶¶0040-0062; ¶0061 (“[T]he sensor output can be calculated using the new calibration curve derived from the recalibration procedure of FIG. 4.”).

e) 23[d]. “and displaying the glucose concentration value.”

110. Zhang discloses the element of claim 23[d].

111. Zhang’s method is for determining and monitoring, and thereby allowing for the management of, a patient’s glucose level, and the POSA would have understood that Zhang’s method involves and/or renders obvious displaying the glucose concentration value for this purpose.

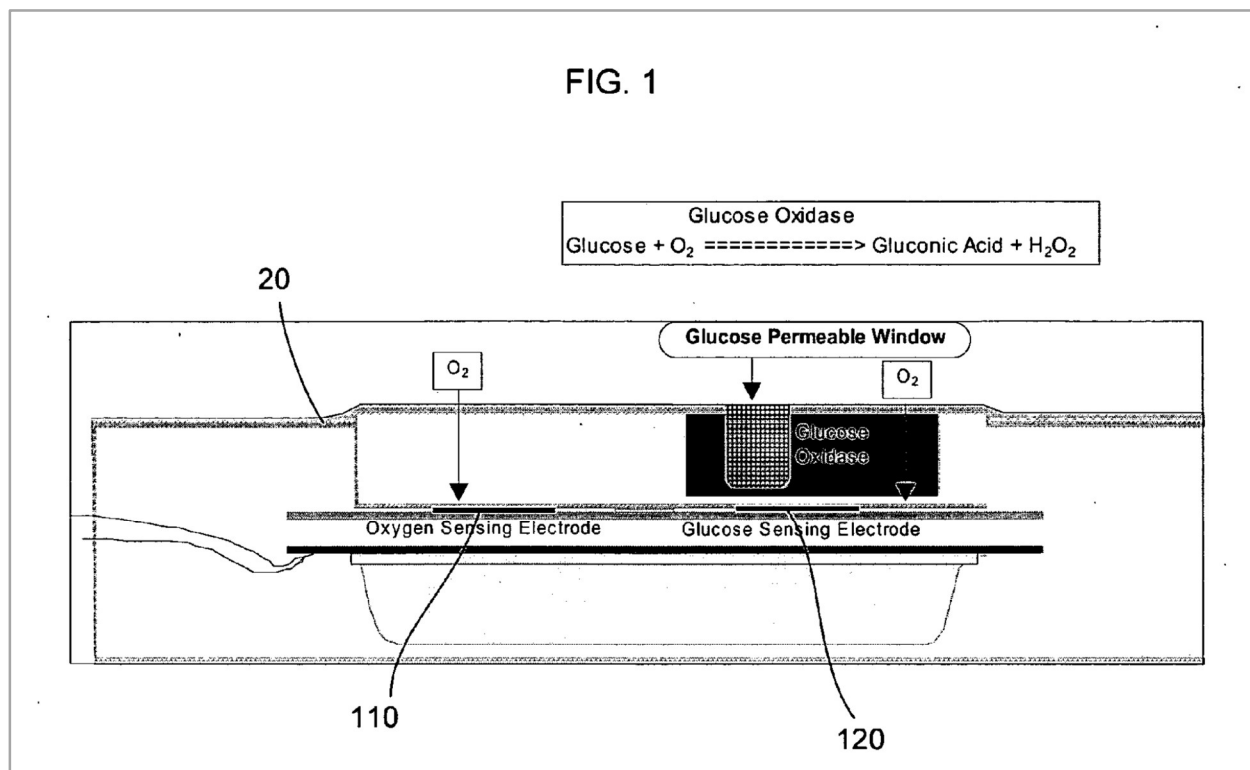
112. For example, Zhang teaches determining and monitoring “a characteristic of a patient’s body,” which in preferred embodiments is “glucose level.” Ex-1004, ¶0027. “[E]mbodiments of the present invention are primarily described in the context of glucose sensors used in the treatment of diabetes,” though they are “applicable to a wide variety of patient treatment programs where a physiological characteristic is monitored.” Ex-1004, ¶0027. Zhang thus teaches monitoring a characteristic such as glucose level for patient treatment programs, including for the treatment of diabetes. The POSA would have understood that, in order for the patient or healthcare provider to respond appropriately to a glucose

concentration value determined by the system and thereby manage the patient's glucose level, the system displays the glucose concentration value. Indeed, commercial CGMs on the market at this time were known to include displays for showing the determined glucose concentration values. Henning (Ex-1025) at 132 (“The electrical measuring apparatus communicates with a device that displays the glucose results using telemetry. ... Besides displaying the most current glucose value, the display device will also show plots of the glucose values over time, alarm settings, and various software menus.”).

2. Claim 24: “The method of claim 23 wherein the in vivo portion of the transcutaneous glucose sensor comprises a substantially planar configuration.”

113. Zhang discloses the method of claim 24.

114. Zhang's sensor has the claimed planar configuration. Ex-1004, FIG. 1:



3. **Claim 25: “The method of claim 23 wherein the drift profile accounts for a break-in of the transcutaneous glucose sensor after the in vivo portion of the transcutaneous glucose sensor has been inserted into the body of the host.”**

115. Claim 25 recites the term “a break-in.” The ’031 patent defines “break-in” broadly to include “electrochemical break-in,” “membrane break-in,” and “sensor break-in.” Further, “sensor break-in” encompasses both “electrochemical break-in” and “membrane break-in.” Ex-1001, 24:50-56, 28:25-30, 29:58-30:6. The patent explains that “sensor break-in” “refers without limitation to the time (after implantation) during which the sensor’s signal is becoming substantially representative of” glucose concentration, and that, “[i]n

some embodiments, sensor break-in occurs prior to obtaining a meaningful calibration of the sensor output.” Ex-1001, 29:60-30:4.

116. Zhang discloses the method of claim 25.

117. Zhang’s profile accounts for “a break-in” of the glucose sensor. The “first phase” (also called “initialization phase”) in Zhang corresponds to “a break-in,” and as discussed above for claim 23, Zhang’s profile includes this first phase of sensor life. Specifically, Zhang explains that first phase, phase 1, is the sensor sensitivity period corresponding to when the sensor “is initially placed in a patient” (Ex-1004, ¶0037) and “becomes used to its environment” (Ex-1004, ¶0032)—i.e., when the sensor is breaking in.

4. Claim 26: “The method of claim 23 wherein the drift profile accounts for a change in sensitivity over time of the in vivo portion of the transcutaneous glucose sensor to the glucose concentration within the body of the host.”

118. Zhang discloses the method of claim 26. *See* discussion of claim 23[c], in section X.A.1.d) (¶¶101-109).

119. Each curve in FIG. 2 corresponds to a different phase of sensor life and reflects the sensor’s sensitivities for a particular phase of sensor life. Zhang’s drift profile (the three curves and the shifts from one curve to another during sensor wear) accounts for the expected sensitivity changes associated with the length of time the sensor has been inserted in the host’s body. Ex-1004, ¶¶0037-0039.

5. Claim 27: “The method of claim 23 wherein the drift profile accounts for a change in baseline over time associated with the in vivo portion of the transcutaneous glucose sensor.”

120. Zhang discloses the method of claim 27. Claim 27 also would have been obvious based on Zhang and the POSA’s knowledge.

121. Zhang’s FIG. 2 shows that at least the curve for phase III (curve 40) has a different baseline from the curves for the earlier phases of sensor life. Zhang also teaches embodiments involving adjustments to the baseline of the calibration curve. Ex-1004, ¶¶0043-0050, ¶¶0061-0062, FIG. 4. Zhang thus teaches embodiments where the shifts in the calibration curve shape are accompanied by changes to the baseline, and Zhang thereby teaches embodiments where “the drift profile accounts for a change in baseline over time,” in addition to a change in sensitivity over time.

122. Claim 27 also would have been obvious based on Zhang and the knowledge in the art that baseline (as well as sensitivity) often shifts over time. E.g., Dock (Ex-1019) at 299 (“Non-linearity of the response, baseline drift and loss of sensitivity with time are common problems with biosensors.”); Frost (Ex-1029) at 636 (“[T]he background signals in the absence of analyte can change appreciably with time for certain amperometric devices.” (citation omitted)). Indeed, Zhang explains that there may be a baseline shift. Ex-1004, ¶¶0043-0046, ¶0061. Accounting for a change in baseline—specifically for expected changes in

baseline—over time in Zhang’s drift profile would have been obvious because Zhang’s drift profile already includes normalized curves, each such curve intercepting the y-axis and thus having a baseline value, and the POSA understood that baseline, like sensor sensitivity, often changes over time. Zhang’s normalized calibration curves (each curve intercepting the y-axis and being associated with a baseline value) would account for changes in baseline (as well as curve shape, and therefore sensor sensitivity) as a sensor progresses through the different phases of sensor life. The different baseline values, like Zhang’s different curve shapes, would be based on empirical data collected from prior sensor use. In other words, baseline changes could be determined based on the same or similar empirical studies of the sensors, similar to how Zhang teaches determining “the calibration curve shapes of each phase of sensor life” “based on empirical data collected from the use of sensors.” Ex-1004, ¶¶0033. Zhang’s drift profile would account for expected changes in baseline, according to baseline changes observed from use of sensors (just like Zhang teaches generating the curve shapes of curves 20, 30 and 40, based on empirical data collected from the prior sensor use). During calibration, baseline adjustments as well as curve shape adjustments would be made based on the expected changes in both baseline and curve shape.

6. **Claim 28: “The method of claim 23 wherein the drift profile accounts for a change in baseline over time associated with the in vivo portion of the transcutaneous glucose sensor and a change in sensitivity over time of the in vivo portion of the transcutaneous glucose sensor to the glucose concentration within the body of the host.”**

123. Zhang discloses and in the alternative renders obvious the method of claim 28. *See* discussion of claims 26 and 27, in sections X.A.4 and X.A.5 (¶¶118-122).

7. **Claim 29: “The method of claim 23 wherein the shift over time is an elapsed time measured from the beginning of the sensor session.”**

124. Zhang discloses the method of claim 29.

125. The shift in sensor sensitivity over time described in Zhang corresponds to a shift over an elapsed time measured from the beginning of the sensor session, which is also the time when the sensor has been inserted into the host.

126. Zhang explains that phase 1 “represents the sensor output when it is initially placed in a patient.” Ex-1004, ¶0037. Zhang teaches calibrating sensor data starting at this time; Zhang teaches that “after a sensor has been implanted into a patient, readings from the sensor need[] to be adjusted for the first phase of the sensor life as the sensor becomes used to its environment.” Ex-1004, ¶0032; ¶¶0031-0062. Zhang thus teaches that the shift in sensor sensitivity over time (during the three phases, and beginning with phase 1 when the sensor is initially

placed in a patient) corresponds to a shift over a time period measured from the beginning of the sensor session.

8. Claim 30: “The method of claim 23 wherein the shift over time is associated at least in part with a change in one or more physical properties of an environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

127. Zhang discloses the method of claim 30 and in the alternative renders claim 30 obvious.

128. In Zhang, the sensitivity changes, exhibited by the shifts between the three normalized curves in FIG. 2 and corresponding to the three phases of sensor life, are associated at least in part with a change in a physical property of the environment surrounding the in-vivo portion of the glucose sensor.

129. Zhang teaches that the curve shape representing each phase and shown in FIG. 2 was determined “based on empirical data collected from the use of sensors.” Ex-1004, ¶0033. At the same time, the POSA understood that the in-vivo environment surrounding the sensor is not constant. For example, it was known that the host’s body reacts to sensor implantation; such host reactions include

inflammatory reactions (which in turn increase temperature) and the migration of cells towards the sensor.⁶

130. In Godek, for example, the author explains that invasive placement of a biomedical device “produces tissue trauma, resulting in the formation of a wound site.” Godek (Ex-1024) at 30.

Since device implantation (or any invasive procedure) produces wounding, inflammation is a natural and known host response to a biomaterial. These events initiate immediately upon device contact with host physiology: with the adsorption of host proteins, surface activation of blood-derived elements including coagulation proteins, complement, and platelets, and progression to the eventual recruitment of inflammatory cells, unresolved wound healing and granulation tissue, and eventual fibrosis. The foreign body reaction (FBR)—the ubiquitous host inflammatory response to implanted

⁶ The '031 patent includes “blockage of sensor surface area due to cells and/or blood clotting at the membrane, biofouling, blood flow/sheer rate, blood pH, [and] temperature” among the physical properties of the sensor or the surrounding fluid that can produce fluctuations in sensitivity and/or baseline. Ex-1001, 143:12-23, claim 31 (reciting “wound healing, blockage of a surface of the transcutaneous glucose sensor, inflammation, blood clotting, or biofouling” as physical properties of an environment surrounding the in-vivo portion of the sensor).

biomaterials—is the consequence of these numerous physiological responses, including aberrant wound healing and inflammation reactions in the presence of an implanted device (e.g., sensors)

Godek (Ex-1024) at 30. As described in Godek, the inflammatory reaction is a “ubiquitous” or inevitable response to sensor insertion. “Notably, no materials or device designs reported to date completely attenuate the FBR, indicating a basal, generic level of host reactivity that may be impossible to eliminate.” Godek (Ex-1024) at 42. *See also* Wisniewski (Ex-1030) at 611 (Fig. 1), 617 (“For many implantable biosensors, the loss of function is also a consequence of inflammation and fibrosis with loss of vasculature resulting from the tissue trauma and long term foreign body response caused by the sensor implantation and by reactions within the tissue.”).

131. It was also known that such host reactions and changes in the environment surrounding the sensor affect sensor sensitivity. For example, as explained in Wilson, “subcutaneously implanted glucose sensors” experience “loss of sensitivity resulting from uptake of species on or into the sensor” following insertion, during the “run-in” period. Wilson (Ex-1023) at 21. Sensor performance is also affected by “the perturbation of oxygen and glucose levels in the tissue surrounding the sensor resulting from tissue injury and the subsequent acute inflammatory response.” Wilson (Ex-1023) at 22. With longer periods of

implantation, “the capsule formation caused by the foreign body reaction may limit the access of glucose and oxygen to the sensor.” Wilson (Ex-1023) at 22; *see also* Godek (Ex-1024) at 42 (“The FBR fibrous capsule provides an adherent, avascular, impermeable barrier often responsible for biomedical device failure or malfunction.” (citations omitted)). *See also* ¶¶43-47, above. Indeed, Zhang repeatedly refers to the sensor’s environment in the discussion of the three phases and thereby recognizes that the sensor’s environment affects sensor sensitivity. Ex-1004, ¶0032, ¶¶0037-0038. *See also* Iyengar (Ex-1016), ¶0059 (Examples of “environmental factors” that “affect the measured electrochemical signal” include “electrode area, extent of electrode fouling, dielectric of the sample, temperature, and ionic concentration of the sample.”),

132. As Zhang teaches that sensor sensitivity changes through the three phases (initialization phase, stable phase, and end-of-life phase), with the curve shape and thus sensor sensitivities of each phase determined empirically, from the testing of sensors, and as the POSA knew that the environment around the sensor is also changing during these phases (with such changes affecting sensitivity and contributing to the observed changes in the curve shape), the POSA would have understood that at least part of the sensitivity changes in the three phases are associated with a change in a physical property of the environment.

133. Claim 30 alternatively would have been obvious in view of Zhang and a POSA's knowledge that environmental changes at the site of sensor implantation affect sensor sensitivity. The POSA would have understood that empirical observations of changes in sensor output with respect to glucose concentration (and therefore sensitivity changes) over time necessarily account for sensitivity changes caused by such environmental changes. The POSA would have found it obvious that Zhang's curve shapes depicting expected sensitivity changes over time, which Zhang expressly teaches were determined empirically, are associated at least in part with a change in a physical property of an environment surrounding the in-vivo portion of the sensor.

9. **Claim 31: "The method of claim 30 wherein the one or more physical properties of the environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host is associated with at least one of: trauma, wound healing, blockage of a surface of the transcutaneous glucose sensor, inflammation, blood clotting, or biofouling."**

134. Zhang discloses the method of claim 31, and in the alternative Zhang renders claim 31 obvious.

135. Claim 31 enumerates causes for the changes in the environment surrounding the in-vivo portion of the sensor. At least some of these causes (e.g., wound healing, inflammation) were known to inevitably occur following insertion of the sensor into the host. *See* discussion above for claim 30, in ¶¶129-131.

Accordingly, the shift over time that is associated at least in part with a change in a

physical property of the environment surrounding the in-vivo portion of the sensor (see claim 30) is necessarily a shift associated with at least one of trauma, wound healing, etc., as recited in claim 31.

136. Claim 31 alternatively would have been obvious, for the same reasons discussed above for claim 30. The POSA would have found it obvious that Zhang's curve shapes depicting expected sensitivity changes over time, which Zhang expressly teaches were determined empirically, are associated at least in part with a change in a physical property of an environment surrounding the in-vivo portion of the sensor, wherein the physical property is associated with trauma, wound healing, blockage of a surface of the transcutaneous glucose sensor, inflammation, blood clotting, and/or biofouling. As discussed above, Godek notes that the host inflammatory response to implanted biomaterials is "ubiquitous" and that "no materials or device designs reported to date completely attenuate" such response. Godek (Ex-1024) at 30, 42.

10. Claim 32: "The method of claim 23 wherein the shift over time is associated at least in part with a physical property of the transcutaneous glucose sensor, wherein the physical property corresponds to a membrane of the in vivo portion of the transcutaneous glucose sensor."

137. Zhang discloses the method of claim 32, and in the alternative Zhang renders claim 32 obvious.

138. As discussed below for claim 35[b], Zhang discloses and/or renders obvious a membrane; the shift over time taught in Zhang and discussed above would have been understood as being associated in part with “a physical property correspond[ing] to a membrane of the in vivo portion” of the sensor, as recited in claim 32.

139. Like the environment surrounding the in-vivo portion of the sensor, the membrane of the sensor also changes over time. It had been well documented that biological materials inevitably become deposited on the membrane; such process was commonly referred to as “membrane biofouling.” *See generally* Wisniewski, which “addresses the effect of membrane biofouling on sensor sensitivity from the standpoint of glucose transport limitations.” Wisniewski (Ex-1030) at 611. “Membrane biofouling is a process that starts immediately upon contact of the sensor with the body when cells, proteins and other biological components adhere to the surface, and in some cases, impregnate the pores of the material.” Wisniewski (Ex-1030) at 612 (citations omitted). It was also well documented that membrane biofouling affects sensor sensitivity. Wisniewski (Ex-1030) at 611 (Fig. 1), 613 (discussing studies showing that membrane biofouling is detrimental to sensor output), 617 (“membrane biofouling play[s] a significant role in sensor instability”). The sensitivity shift over time taught in Zhang, which is

based on empirical data, must be, or would have been understood as being, associated at least in part with membrane biofouling.

140. Alternatively, the POSA would have found it obvious that Zhang's curves and shifts in sensitivity over time are associated with a change in a physical property of the membrane, especially in light of the observation that "[m]embrane biofouling is a process that starts immediately upon contact of the sensor with the body when cells, proteins and other biological components adhere to the surface, and in some cases, impregnate the pores of the material." Wisniewski (Ex-1030) at 612 (citations omitted). The POSA would have found it obvious to have Zhang's curve shapes account for changes in sensor output that were known to occur, including changes due to membrane biofouling.

11. Claim 33: "The method of claim 23 wherein the shift over time is an elapsed time measured from the insertion of the in vivo portion of the transcutaneous glucose sensor within the body of the host."

141. Zhang discloses the method of claim 33.

142. The shift over time reflected in Zhang's drift profile corresponds to an elapsed time measured from the insertion of the sensor into the host's body. Zhang explains that sensor output during phase 1, shown by line 20 during this first phase, "represents the sensor output when it is initially placed in a patient." Ex-1004, ¶0037. Zhang also teaches that sensor output is calibrated at this time. Ex-1004, ¶¶0031-0062. Thus Zhang teaches that the subsequent shift(s) in curve shape (and

thus sensor sensitivity) over time corresponds to a time period measured from the insertion of the sensor into host's body.

12. Claim 34: “The method of claim 23 wherein the drift profile has a first slope associated with a first time and a second slope associated with a second time, wherein the first time is different from the second time, wherein the first slope is different from the second slope.”

143. Zhang discloses the method of claim 34.

144. As explained above with respect to claim 23[c], each of Zhang's three normalized curves has a slope or slopes that differ from the slope(s) of the other curves, and each curve is associated with a different time period (phase I, phase II, and phase III, respectively) of sensor life. Ex-1004, ¶¶0033, ¶¶0037-0039. *See* ¶¶104-106, above.

13. Independent claim 35

a) 35[Pre]. “A sensor system comprising:”

145. To the extent the preamble is limiting, Zhang discloses it. Zhang describes a system comprising a sensor to monitor glucose concentration. Ex-1004, ¶¶0008, ¶¶0015, ¶¶0027.

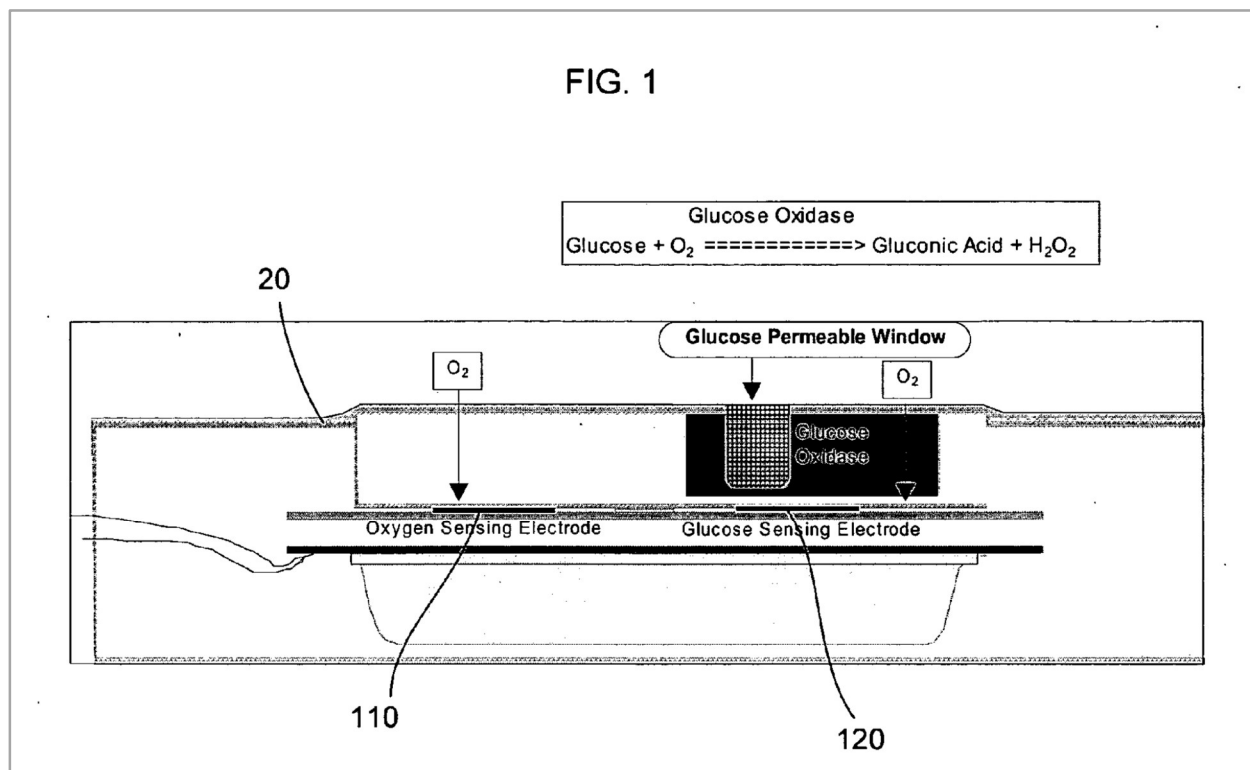
- b) **35[a]. “a transcutaneous glucose sensor comprising: an ex vivo portion configured to remain outside of a body of a host; and an in vivo portion configured to be implanted within the body of the host,”**

146. Zhang discloses the element of claim 35[a], and in the alternative Zhang renders claim element 35[a] obvious. *See* discussion of claim 23[a], in section X.A.1.b) (¶¶94-98).

- c) **35[b]. “wherein the in vivo portion comprises: an electrode; and a membrane disposed over at least a portion of the electrode, wherein the membrane comprises at least one enzyme;”**

147. Zhang discloses the element of claim 35[b], and in the alternative Zhang renders the claim element obvious.

148. Zhang describes a glucose sensor that comprises an electrode and that relies on the glucose oxidase enzyme to detect the level of glucose. Ex-1004, ¶¶0028-0029, FIG. 1:



149. As shown in FIG. 1, the enzyme glucose oxidase is contained within a specific region of the sensor. The POSA would have understood that, for the enzyme to be contained as shown, the enzyme is immobilised. The POSA further would have reasonably understood that the enzyme is contained in the area shown using a material that immobilises the enzyme while also allowing glucose to diffuse into the area and the enzyme to catalyze the reaction between glucose and

oxygen; the POSA would have understood such material to be a “membrane.”⁷

Additionally, the area containing the enzyme is over the glucose sensing electrode.

150. Zhang also incorporates by reference several documents that disclose glucose sensors having an electrode with a membrane disposed thereon, wherein

⁷ Claim 35[b] recites the term “membrane.” The ’031 patent does not define the term “membrane.” The patent however consistently uses the term to encompass a material or layer that controls the diffusion of substances (e.g., oxygen, glucose, hydrogen peroxide) and/or stabilises and immobilises the enzyme. *E.g.*, Ex-1001, 103:20-25 (The sensor may comprise “a sensor membrane configured to substantially block diffusion of at least one of an analyte and a co-analyte between the first and second working electrodes...”), 121:63-122:3 (“[T]he diffusion barrier can be a bioprotective membrane (e.g., a membrane that substantially resists, attenuates or blocks the transport of a species (e.g., hydrogen peroxide), such as a polyurethane. As yet another example, the diffusion barrier can be a resistance domain, ... namely, a semipermeable membrane that controls the flux of oxygen and an analyte (e.g., glucose) to the underlying enzyme domain.”), 129:3-5 (“[T]he physical diffusion barrier” can be “formed of one or more membrane materials.”); *see also* Ex-1001, 86:49-45. Such usage of the term “membrane” is consistent with how the term was and is used in the art.

the membrane comprises an enzyme. Zhang in ¶0028 incorporates by reference Patent Nos. 4,650,547 (Ex-1005) and 4,703,756 (Ex-1006), each of which describes glucose sensors having an electrode with a membrane comprising an enzyme. E.g., Ex-1005, 6:3-41, FIG. 5; Ex-1006, 3:13-15 (The “sensor contacts glucose oxidase which is impregnated in a membrane and disposed about the sensor.”), 4:27-36.

151. Containing the glucose oxidase in a membrane that is disposed over at least a portion of the electrode also would have been obvious based on CGMs described in the art and on the knowledge of how those CGMs generally operate. CGMs commonly employed the enzyme glucose oxidase, which required containment or immobilisation, and a preferred technique in the art for containing or immobilising enzymes, and the technique used in commercial systems, was with the use of a membrane. For example, Koudelka-Hep explains that, “[i]n the vast majority of sensors,” the glucose oxidase “is immobilised by glutaraldehyde cross-linking” to form “gel-like membranes having good mechanical stability and thickness of several μm .” Koudelka-Hep (Ex-1021) at 60. Similarly, Henning refers to the “enzyme-containing membrane that covers the metal conductor” of the “working electrode of the sensor” as one of the components common to commercial CGMs. Henning (Ex-1025) at 132. Notably, Henning describes

commercial CGMs as having an “enzyme-containing membrane” without noting any exceptions. *See* ¶32, above.

152. The commonplace use of an enzyme-containing membrane in glucose sensors is also discussed in patent literature. *See, e.g.,* Say (Ex-1011) at 16:6-40 (“The sensing layer 64 may be formed as a solid composition of the desired components (e.g., an electron transfer agent and/or a catalyst). ***These components are preferably non-leachable from the sensor 42 and more preferably are immobilized on the sensor 42.*** For example, the components may be immobilized on a working electrode 58. Alternatively, ***the components of the sensing layer 64 may be immobilized within or between one or more membranes or films disposed over the working electrode 58*** or the components may be immobilized in a polymeric or sol-gel matrix.”) (emphases added), 20:48-52 (“Preferably, the catalyst [such as glucose oxidase, *see* Say, 20:31-40] is non-leachably disposed on the sensor, whether the catalyst is part of a solid sensing layer in the sensor or solvated in a fluid within the sensing layer. More preferably, ***the catalyst is immobilized within the sensor (e.g., on the electrode and/or within or between a membrane or film) to prevent unwanted leaching of the catalyst away from the working electrode 58 and into the patient.***” (emphasis added)).

153. The POSA would have been motivated to use such technique (i.e., a membrane), and thereby would have been motivated to use a sensor as recited in

claim 35[b], and would have reasonably expected success in doing so, at least because using a membrane to immobilise the enzyme had been practiced successfully in commercial and other systems described in the art.

154. In addition, it was known that the concentration of oxygen is generally lower than the concentration of glucose, such that oxygen can be a rate-limiting substrate (in the reaction catalyzed by glucose oxidase discussed above in ¶30), affecting sensor measurements; the art had taught that membranes with differential permeabilities to oxygen and glucose are useful to control the diffusion rate of glucose and thereby address this issue. *See, e.g.,* Alcock (Ex-1028) at 321 (“Oxygen independence is an important consideration for *in vivo* sensors. In subcutaneous tissue, the concentration of oxygen can be considerably lower than that of glucose, and hence oxygen can be a rate-limiting substrate. Membranes with differential permeabilities to oxygen and glucose have been incorporated in sensor design to overcome this limitation.”). While a membrane with differential permeability to oxygen and glucose could be a membrane separate from the enzyme-containing membrane, sensors containing such a membrane typically also had an enzyme membrane and therefore multiple membranes or layers. *E.g.,* Wilson (Ex-1023) at 11-12 (*e.g.,* Figure 1.1); Frost (Ex-1029) at 635-636 (describing the use of membranes to control analyte mass transfer, and describing a

sensor design having “multiple membrane coatings and electrodeposition of the glucose oxidase layer”).

155. Accordingly, Zhang discloses, or alternatively renders obvious, a sensor as recited in claim 35[b].

d) 35[c]. “wherein the transcutaneous glucose sensor generates a signal associated with a glucose concentration within the body of the host;”

156. Zhang discloses the element of claim 35[c]. Zhang’s glucose sensor is configured to generate a signal (current), the magnitude of which depends on glucose concentration.

157. Specifically, Zhang describes a sensor “designed to send a particular current depending on the amount of oxygen present near” an “oxygen sensing electrode 110” and a “glucose sensing electrode 120 placed in the proximity of glucose oxidase to ascertain the oxygen depletion” around the sensor, and thus the amount of glucose present, based on a “fairly linear relationship” between oxygen and current. Ex-1004, ¶0029 (“a measurement of the currents can be used to determine the amount of glucose present in the blood”). Zhang explains:

Typically, the glucose sensor 20 has at least two electrodes 110, 120 to detect the level of oxygen in the blood. Preferably, the first electrode is an oxygen sensing electrode 110 to detect the level of oxygen in the patient fluid (e.g. blood) as a reference point for the second electrode. *The second electrode is a glucose sensing*

electrode 120 placed in the proximity of glucose oxidase to ascertain the oxygen depletion during the electrochemical reaction between oxygen and the glucose around the area of the glucose sensing electrode 120. The glucose oxygen sensor 20 is designed *to send a particular current depending on the amount of oxygen present near the electrodes 110, 120*. Given that the amount of current flowing to the electrodes has a fairly linear relationship the amount oxygen present in the area surrounding the electrodes 110, 120, *a measurement of the currents can be used to determine the amount of glucose present in the blood, ...*

Ex-1004, ¶0029 (emphases added).

158. Zhang also describes a hydrogen peroxide sensor that “measure[s] the amount of hydrogen peroxide produced as a result of the reaction between oxygen and glucose in the presence of the glucose oxidase enzyme.” Ex-1004, ¶0030.

e) 35[d]. “electronics configured to receive the signal from the transcutaneous glucose sensor,”

159. Claim 35[d] recites the term “electronics.” The ’031 patent states “electronics” and “sensor electronics” are “broad terms” and “refer without limitation to electronics operatively coupled to the sensor and configured to measure, process, receive, and/or transmit data associated with a sensor.” Ex-1001, 25:13-20; *see* Ex-1001, 25:13-37.

160. Zhang discloses the element of claim 35[d]. Zhang's system comprises electronics configured to receive signals from the glucose sensor. Claim element 35[d] also would have been obvious.

161. In Zhang's systems, sensor readings are processed in a calibration method as described above. Ex-1004, ¶¶0037-0063. For sensor readings to be processed (i.e., calibrated), Zhang's system comprises electronics configured to receive the signals from the sensor. Indeed, Zhang discloses "a processor connected to the sensor for processing" the sensed parameter. Ex-1004, ¶0013. The processor thus comprises electronics configured to receive sensor signals.

162. Zhang in ¶0029 also incorporates by reference Morgan's disclosure. Morgan "relates to the field of sensor electronics" (Morgan (Ex-1007), ¶0003) and discusses electronics (a "data converter") configured to receive sensor signals. E.g., Morgan (Ex-1007), FIGS. 1, 5, ¶0010, ¶0013, ¶0027, ¶0034, ¶0036, ¶¶0038-39, ¶0043.

163. This claim element also would have been obvious in view of the POSA's knowledge of CGMs and their basic components, which included electronics that receive sensor signals and that perform functions such as processing the signals received from the sensor, as evidenced by various prior art.

164. Shin, for example, describes a glucose monitoring system that includes a glucose monitor and a processor, where in certain embodiments "[t]he

glucose monitor 100 generally includes the capability to record and store data as it is received from the glucose sensor 12, and includes either a data port (not shown) or wireless transmitter and/or receiver (also not shown) for transferring data to and/or from a data processor 200” Shin (Ex-1008), ¶0058; *see also* Shin (Ex-1008), ¶0061 (“In alternative embodiments, the glucose monitor includes at least portions of the software described as contained with the data processor 200 above. The glucose monitor might contain the necessary software to calibration glucose sensor signals”). *See also* Shin (Ex-1008), ¶0015 (“the processor is in a separate device that receives glucose monitor data from the glucose monitor”). *See also* Mastrototaro (Ex-1010) (describing embodiments of systems and methods similar to Shin’s systems and methods); Breton (Ex-1014), ¶¶0036-0047.

165. Say similarly describes analyte monitoring systems with electronics configured to receive signals from the sensor. For example, Say’s system includes a display unit that has “a receiver for receiving data transmitted by the transmitter of the sensor control unit.” Say (Ex-1011), Abstract; *see also* Say, 2:45-51 (“The analyte monitoring system also includes a display unit that has a receiver for receiving data from the sensor control unit and a display coupled to the receiver for displaying an indication of the level of an analyte.”), 40:23-27, 41:10-53 (describing signals sent by the transmitter to the “receiver/display units”), FIGS. 22-24. Say also describes embodiments where receiver electronics may be

contained in the on-skin control unit. Specifically, Say describes an embodiment where the on-skin control unit “includes optional components such as a receiver 99 to receive, for example, calibration data; a calibration storage unit 100 to hold, for example, factory-set calibration data, calibration data obtained via the receiver 99 and/or operational signals received, for example, from a receiver/display unit 46, 48 or other external device” Say (Ex-1011), 37:26-33; *see also* Say, 2:26-32 (explaining the “sensor control unit” may include “a variety of optional components,” including “a receiver”). *See also* Heller-2003 (Ex-1017), 7:1-18, 50:2-11; Feldman (Ex-1012), ¶¶0063-0065.

166. See also Henning (Ex-1025) at 131-132, which explains that “[a]ll the on-market CGM devices have similar components,” and that such components include a device that communicates with and receives data from an electrical measuring apparatus and that therefore contains receiver electronics. Specifically, the author explains: “Electrical contact is made from the sensor to an electrical measuring apparatus, the potentiostat. ... The electrical measuring apparatus communicates with a device that displays the glucose results using telemetry. ...

The display device will have a large memory typically capable of recording glucose results of months.” Henning (Ex-1025) at 132.⁸

f) 35[e]. “wherein the electronics comprises a memory, wherein the memory stores information associated with an expected change over time in a relationship between the signal and the glucose concentration within the body of the host,”

167. Zhang discloses the element of claim 35[e]. Electronics with memory storing calibration information also would have been obvious.

168. Zhang’s electronics comprises a memory—the memory stores “the expected normalized calibration curves” generated using the a priori, empirical data and that are used in processing (i.e., calibrating) sensor readings. Ex-1004, ¶¶0015-0016 (describing generating a calibration curve using a priori values), ¶0033 (explaining “the calibration curve shapes of each phase of the sensor life” shown in FIG. 2 are “based on empirical data collected from the use of the sensors”), claims 34, 36; *see also* Ex-1004, ¶0007, ¶0013 (describing “an array of data” and “adjusting a curve representing the sensor output based on data in the

⁸ In its definition of “electronics” and “sensor electronics,” the ’031 patent states that “[i]n some embodiments, the sensor electronics include a transmitter that transmits the signals from the potentiostat to a receiver” Ex-1001, 25:13-38.

array”). To use pre-generated normalized calibration curves when processing sensor readings, the electronics must comprise a memory for storing such curves.

169. Glucose monitoring systems comprising electronics with memory also would have been obvious. Shin and Say, for example, each describe this basic configuration of glucose monitoring systems.

170. As discussed below for Shin, Shin discloses “electronics” that includes a “glucose monitor” and a “data processor.” Shin describes embodiments where the glucose monitor stores the information for calibrating sensor data, and describes alternative embodiments where the data processor stores the information for calibrating sensor data. Ex-1008 (Shin), ¶¶0058-0060. In either case, the system comprises electronics with memory and that operably connect to the glucose sensor. *See* ¶¶274-276, below.

171. Say also discloses a glucose monitoring system comprising electronics configured to receive signals from the sensor, wherein the electronics comprises a memory. 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. Say (Ex-1011), 43:36-44, FIGS. 18A, 18B. *See also* Say (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”).

172. The normalized calibration curves stored in Zhang’s memory are “information associated with an expected change over time in a relationship between the signal and the glucose concentration within the body of the host,” as recited in claim 35[e]. Zhang’s normalized curves account for expected changes in sensor sensitivity over time, and such expected sensitivity changes are information associated with an expected change over time in a relationship between the signal and the glucose concentration.

173. As explained above, each of the three curves in Zhang’s FIG. 2 has a different shape, the different shapes showing that each phase of sensor life is associated with different sensor sensitivities. These three curves, and their associated sensitivities, show the change over time in sensor sensitivity, which results in a “change over time in a relationship between the signal and the glucose concentration within the body,” as recited in claim 35[e]. *See* discussion in ¶¶38-42 (Technology Background).

174. In addition, the curves in FIG. 2 were determined “based on empirical data collected from the use of the sensors” (Ex-1004, ¶0033) and thus are pre-determined and reflect “expected” changes over time. *See also* Ex-1004, ¶0016 (referring to “a priori empirical values of sensors similar to the sensor being

calibrated”).⁹ The curves therefore show “expected” changes over time, as required by claim 35[e].

g) **35[f]. “wherein the electronics is configured to generate a glucose concentration value based at least in part on the signal and the information associated with the expected change over time in the relationship.”**

175. Zhang discloses the element of claim 35[f].

176. *See* discussion of claim 23[c], in section X.A.1.d) (¶¶101-109).

Zhang’s system (the electronics therein) determines a glucose concentration based at least in part on the sensor signal and the normalized calibration curves. Zhang teaches that “sensor recalibrations will be performed not only based on independent characteristic values (e.g., blood meter values) but with use of the expected normalized calibration curves.” Ex-1004, ¶0033. The sensor recalibrations are used in determining a glucose concentration. Ex-1004, ¶0029,

⁹ I have been informed that, in a co-pending district court litigation, DexCom has asserted, in its infringement contentions, that the challenged claims encompass embodiments where information on the “expected” change over time is obtained from prior studies involving only sensors other than the sensor in the claimed system or other than the sensor being calibrated. For the purpose of this declaration, I have applied DexCom’s interpretation of the claims.

¶¶0033-0035, ¶¶0040-0062; Ex-1004, ¶0061 (“[T]he sensor output can be calculated using the new calibration curve derived from the recalibration procedure of FIG. 4.”).

- 14. Claim 36: “The sensor system of claim 35 wherein the change over time in the relationship is associated at least in part with a change in one or more physical properties of an environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host.”**

177. Zhang discloses the sensor system of claim 36 and in the alternative renders claim 36 obvious.

178. *See* discussions of claims 30 and 35[e], in sections X.A.8 (¶¶127-133) and X.A.13.f) (¶¶167-174), which explain how Zhang’s curve shape adjustments account for a shift or change over time in sensor sensitivity, such change being associated at least in part with a change in a physical property of the in-vivo environment surrounding the sensor.

- 15. Claim 37: “The sensor system of claim 36, wherein the one or more physical properties of the environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host include trauma, wound healing, blockage of a surface of the transcutaneous glucose sensor, inflammation, blood clotting, or biofouling.”**

179. Zhang discloses the sensor system of claim 37 and in the alternative renders claim 37 obvious.

180. *See* discussion of claim 31, in section X.A.9 (¶¶134-136).

16. Claim 38: “The sensor system of claim 35 wherein the change over time in the relationship is associated with the implantation of the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

181. Zhang discloses the sensor system of claim 38, and in the alternative Zhang renders claim 38 obvious.

182. As discussed above for claims 30 and 31, it was known that the host’s body reacts to sensor implantation, and that such reactions affect sensor sensitivity. Because Zhang’s three curve shapes are empirically-determined, they are associated with the expected changes in sensor sensitivity that inevitably accompany sensor implantation. *See* section X.A.8 (¶¶127-133) and section X.A.9 (¶¶134-136), discussing claims 30 and 31, respectively.

183. Alternatively, it would have been obvious to account for changes in the relationship that result from such reactions. As discussed previously, that sensor sensitivity changes following sensor insertion was well-documented in the art. *See* ¶¶43-47. The POSA, having a desire to improve calibration methods and improve the accuracy of glucose monitoring systems, would have sought to account for such changes, including the changes that inevitably occur as a result of host reactions to sensor insertion. Zhang provided the POSA with a system and method for accounting for such changes.

17. Claim 39: “The sensor system of claim 35 wherein the change over time in the relationship is over an elapsed time measured from a beginning of a sensor session after implantation of the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

184. Zhang discloses the sensor system of claim 39.

185. *See* discussion of claim 29, in section X.A.7 (¶¶124-126).

18. Claim 40: “The sensor system of claim 35 wherein the change over time in the relationship is over an elapsed time measured from the implantation of the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

186. Zhang discloses the sensor system of claim 40.

187. *See* discussion of claim 33, in section X.A.11 (¶¶141-142).

19. Claim 41: “The sensor system of claim 35 wherein the change over time in the relationship is associated at least in part with a physical property of the transcutaneous glucose sensor, wherein the physical property of the transcutaneous glucose sensor corresponds to membrane of the in vivo portion of the transcutaneous glucose sensor.”

188. Zhang discloses the sensor system of claim 41, and in the alternative Zhang renders claim 41 obvious.

189. *See* discussion of claim 32, in section X.A.10 (¶¶137-140).

20. Independent claim 42

a) 42[Pre]. “A method for monitoring a glucose concentration, the method comprising:”

190. To the extent the preamble is limiting, Zhang discloses it. Zhang describes a method of monitoring glucose concentration. Ex-1004, ¶0007

(describing a “method for calibrating a sensor”), ¶0008 (referring to “glucose electrode readings”), ¶0014 (“The sensor may be a glucose sensor.”), ¶0027 (“Embodiments of the present invention are directed to calibration techniques for use with implantable sensors that measure a characteristic of a patient’s body. In preferred embodiments, the characteristic is the glucose level....”).

- b) **42[a]. “beginning a sensor session associated with use of a transcutaneous glucose sensor, wherein the transcutaneous glucose sensor comprises: an ex vivo portion configured to remain outside of a body of a host; and an in vivo portion configured to be inserted within the body of the host;”**

191. Zhang discloses the element of claim 42[a] and in the alternative renders claim element 42[a] obvious.

192. Zhang describes beginning a sensor session as claimed. Zhang describes methods for calibrating glucose sensor data, where the sensor readings are adjusted as described above (*see* section X.A.1.d) (¶¶101-109, discussing claim 23[c])). By teaching obtaining and then processing sensor output, Zhang teaches beginning a sensor session. *See* discussion of claim 23[a], in section X.A.1.b) (¶¶94-98), for elements concerning the sensor itself.

- c) **42[b]. “wherein the transcutaneous glucose sensor is configured to generate a signal;”**

193. Zhang discloses the element of claim 42[b].

194. Zhang's glucose sensor is configured to generate a signal. The electrodes of the sensor, which are implanted in the user, generate current. Ex-1004, ¶¶0029 ("a measurement of the currents can be used to determine the amount of glucose present in the blood"), ¶¶0042-0062 (referring to "glucose electrode readings" and "nominal glucose current"). *See* discussion of claims 35[d] and 35[f], in sections X.A.13.e) (¶¶159-166) and X.A.13.g) (¶¶175-176), respectively.

d) 42[c]. "calibrating the transcutaneous glucose sensor by applying a priori information, wherein the a priori information comprises an expected relationship between the signal and a glucose concentration existing within the body of the host, wherein the relationship changes as a function of time;"

195. Zhang discloses the element of claim 42[c].

196. Zhang's method involves calibrating the sensor by applying a priori information. The method involves using "a priori information" that comprises "an expected relationship between the signal and a glucose concentration existing within the body of the host, wherein the relationship changes as a function of time," as recited by claim 42[c].

197. As discussed above, Zhang's calibration method adjusts the calibration curve shape over time, and each adjustment changes the curve slope(s), and in this way Zhang's method accounts for sensor sensitivity changes over time. *See* section X.A.1.d) (¶¶101-109, discussing claim 23[c]), section X.A.13.g) (¶¶175-176, discussing claim 35[f]), and ¶¶78-81 (discussing Zhang's calibration

method). Zhang's three curve shapes and the adjustment from one curve shape to another (from the curve shape for phase I, to the curve shape for phase II, to the curve shape for phase III, each adjustment accounting for expected changes in sensor sensitivity over time) comprise "an expected relationship between the signal and a glucose concentration existing within the body of the host, wherein the relationship changes as a function of time," as recited in claim 42[c].¹⁰

198. In addition, Zhang's three curve shapes are determined from empirical data collected from use of the sensors (Ex-1004, ¶0033, ¶0016) and thus are "a priori information." This a priori information is applied to the sensor, to calibrate the sensor. Ex-1004, ¶0033, ¶0040. Zhang thus describes calibrating the sensor by "applying a priori information," wherein the a priori information comprises "an expected relationship" as recited in claim 42[c].

e) 42[d]. "generating a glucose concentration value based at least in part on the calibrating; and"

199. Zhang discloses the element of claim 42[d].

¹⁰ See Ex-1001, 216:47-52: "For example, during the first hour of sensor use, the expected profile may be a line having a slope and/or curvature within a first range; while during the second hour of use the expected profile may be a line having a slope and/or curvature within a second range."

200. See discussion of claims 23[c] and 35[f], in sections X.A.1.d) (§§101-109) and X.A.13.g) (§§175-176), respectively. See also §§78-81 (describing Zhang's calibration method).

f) 42[e]. “displaying the glucose concentration value.”

201. Zhang discloses the element of claim 42[e].

202. See discussion of claim 23[d], in section X.A.1.e) (§§110-112).

21. Claim 43: “The method of claim 42 wherein the time the relationship changes is an elapsed time measured from the beginning of the sensor session.”

203. Zhang discloses the method of claim 43.

204. See discussion of claim 29, in section X.A.7 (§§124-126).

22. Claim 44: “The method of claim 42 wherein the time the relationship changes as a function of time is associated at least in part with a change in one or more physical properties of an environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

205. Zhang discloses the method of claim 44 and in the alternative renders claim 44 obvious.

206. See discussion of claim 30, in section X.A.8 (§§127-133).

- 23. Claim 45: “The method of claim 44 wherein the one or more physical properties of the environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host include trauma, wound healing, blockage of a surface of the transcutaneous glucose sensor, inflammation, blood clotting, or biofouling.”**

207. Zhang discloses the method of claim 45 and in the alternative renders claim 45 obvious.

208. See discussion of claim 31, in section X.A.9 (§§134-136).

- 24. Claim 46: “The method of claim 42 wherein the time the relationship changes as a function of time is associated at least in part with a physical property of the transcutaneous glucose sensor, wherein the physical property of the transcutaneous glucose sensor corresponds to a membrane of the in vivo portion of the transcutaneous glucose sensor.”**

209. Zhang discloses the method of claim 46 and in the alternative renders claim 46 obvious.

210. See discussion of claim 32, in section X.A.10 (§§137-140).

B. Shin Anticipates and/or Renders Obvious Claims 23-46 of the '031 Patent

211. Claims 23-46 of the '031 patent are anticipated by Shin (Ex-1008), and/or are rendered obvious by Shin in view of the POSA's knowledge. An overview of Shin is provided above. My specific analysis of Shin for every element of claims 23-46 is provided below.

1. Independent Claim 23

a) 23[Pre]. “A method for monitoring a glucose concentration, the method comprising:”

212. To the extent the preamble is limiting, it is disclosed in Shin. Shin describes a method for monitoring glucose concentration in a host. E.g., Ex-1008, ¶0054 (“In preferred embodiments of the present invention, the sensor and monitor are a glucose sensor and a glucose monitor for determining glucose levels in the blood and/or bodily fluids of a user.”).

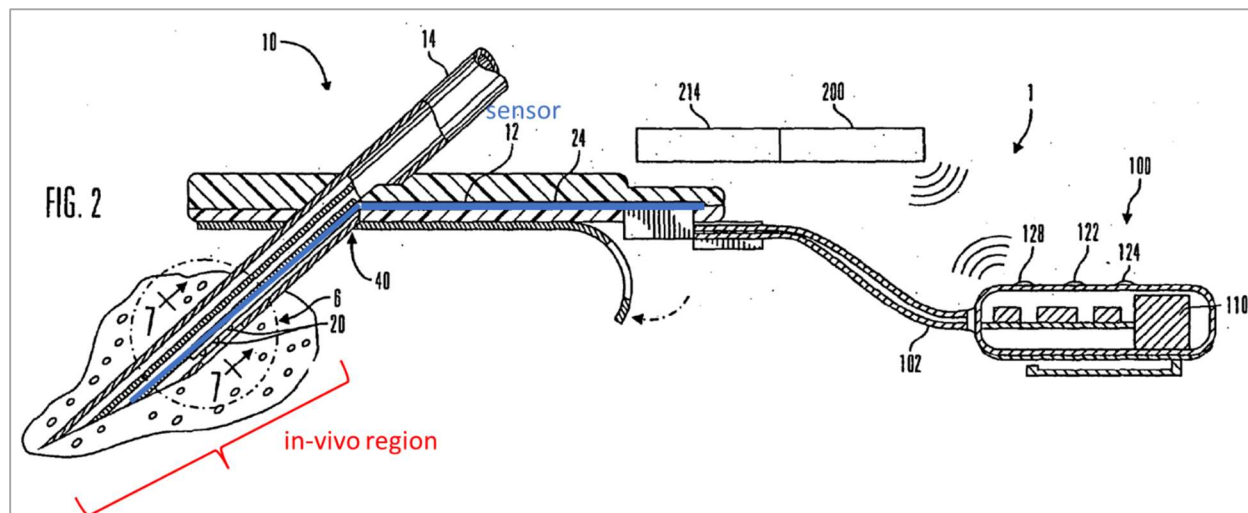
b) 23[a]. “beginning a sensor session associated with use of a transcutaneous glucose sensor, wherein the transcutaneous glucose sensor comprises: an ex vivo portion configured to remain outside of a body of a host; and an in vivo portion configured to be inserted within the body of the host;”

213. Shin discloses the element of claim 23[a].

214. Shin teaches beginning a sensor session with a transcutaneous glucose sensor, as recited in claim 23[a]. E.g., Ex-1008, ¶0006 (“[A] method of calibrating glucose monitor data includes obtaining glucose monitor data at predetermined intervals over a period of time.”).

215. Shin’s glucose sensor 12 “extends from the glucose sensor set 10 into the user’s body with electrodes 20 of the glucose sensor 12 terminating in the user’s subcutaneous tissue.” Ex-1008, ¶0057. FIG. 2 illustrates both the in-vivo and ex-vivo portions of the sensor. The in-vivo portion of the sensor extends into

in-vivo “region 6” shown in FIG. 2, which is reproduced below with annotations in blue (for the sensor) and red (for the in-vivo region):



As shown above, a portion of the sensor 12 remains with the sensor set 10 and thus outside of the user's body.

216. As shown in the annotated figure above, a portion of the glucose sensor 12 is inserted through the skin, and another portion of the glucose sensor 12 remains with the sensor set 10 and thus outside of the user's body. Thus the glucose sensor 12 comprises “an ex vivo portion configured to remain outside of a body of a host; and an in vivo portion configured to be inserted into the body of the host,” as recited in claim 23[a].

c) 23[b]. “generating sensor data derived at least in part from the transcutaneous glucose sensor;”

217. Shin discloses the element of claim 23[b].

218. In Shin, “the glucose monitor 100 measures a continuous electrical current signal (ISIG) generated by the glucose sensor 12 relative to a concentration of glucose present in the subcutaneous tissue of the user’s body.” Ex-1008, ¶0069.

- d) **23[c]. “determining a glucose concentration value based at least in part on the sensor data and information associated with a drift profile, wherein the drift profile is associated with a shift over time in measurement [sic] characteristic of the transcutaneous glucose sensor to the glucose concentration within the body of the host resulting from the in vivo portion of the transcutaneous glucose sensor being within the body of the host for a period of time;”**

219. Shin discloses the element of claim 23[c].

220. Shin teaches calibrating sensor data and determining a glucose concentration value, using predetermined valid sensitivity ranges that are based on how long the sensor has been in use. In Shin’s calibration method, the calibration factor (each calculated modified single-point sensitivity ratio (MSPSR) (Ex-1008, ¶0093)) is compared to a pre-determined valid sensitivity range, and the valid sensitivity ranges used over time can be ranges that depend on how long the sensor has been in use (Ex-1008, ¶0103)—i.e., the ranges are “a drift profile.” As a result of this comparison, the system either accepts or rejects the MSPSR for calibration and the determination of a glucose concentration value. In this way, Shin discloses determining a glucose concentration value based at least in part on sensor data and on “information associated with a drift profile, wherein the drift profile is

associated with a shift over time in measurement characteristic of the” sensor, as recited in claim 23[c].

221. Specifically, Shin teaches that each MSPSR is compared to “a valid sensitivity range” to determine if it is reasonable. Ex-1008, ¶0103. Shin provides a particular valid MSPSR range of 1.5 to 15 that “has been determined based upon valid glucose sensor sensitivity measurements made in-vitro” and further explains that “[o]ther valid sensitivity ranges may be applied depending on ... how long the sensor has been in use.” Ex-1008, ¶0103. Thus, in embodiments of Shin, the calibration factor (the MSPSR) is compared to “valid sensitivity ranges,” and such ranges can depend on “how long the sensor has been in use.”

222. Shin’s valid sensitivity ranges that depend on how long the sensor has been in use constitute “a drift profile” (and thus also “information associated with a drift profile” as recited in claim 23[c]) wherein the drift profile is associated with a shift over time in a measurement characteristic of the sensor (in this case, sensor sensitivity) resulting from the sensor being within the host’s body for a period of time, as recited in claim 23[c]. In Shin, different valid sensitivity ranges can be used, each range associated with a length of time of sensor use; thus the ranges relate to expected sensitivity changes over time, during sensor use. Such valid sensitivity ranges that depend on the length of time of sensor use constitute “a drift profile.” *Compare* Ex-1008, ¶0103 to Ex-1001, 213:5-43 (e.g., 213:33-36 (“[T]he a

priori sensitivity information includes and/or provides an expected profile (e.g., an expected pattern and/or amount of sensitivity change/drift over time).... In some embodiments, the a priori sensitivity information defines a range (e.g., within boundaries and/or guard bands) of acceptable change (increase and/or decrease) in sensitivity.”)), 216:44-61 (e.g., 216:48-56: “[D]uring the first hour of sensor use, the expected profile may be a line having a slope and/or curvature within a first range; while during the second hour of use the expected profile may be a line having a slope and/or curvature within a second range. In some embodiments, the a priori sensitivity information defines a range of acceptable change in sensitivity, such as described with reference to a cone of possible acceptable and/or feasible sensitivity changes.”).

e) 23[d]. “and displaying the glucose concentration value.”

223. Shin discloses the element of claim 23[d].

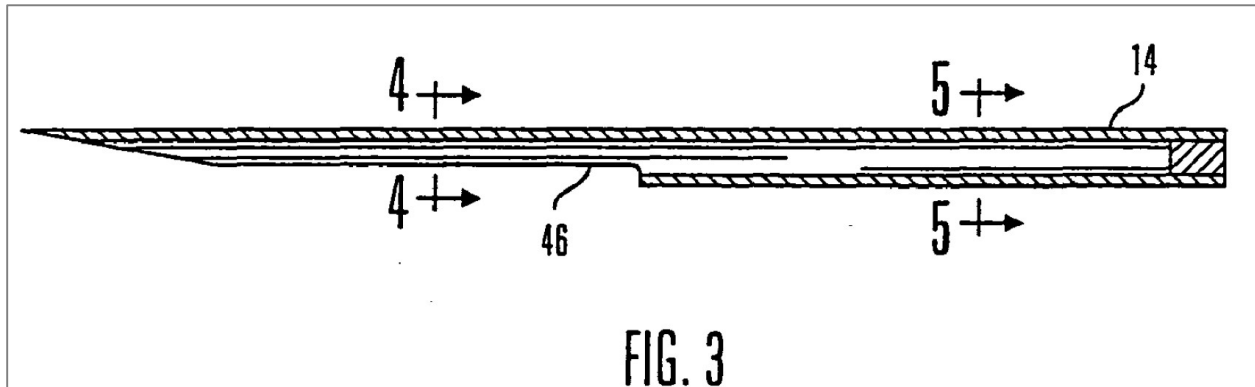
224. Shin’s method involves displaying the determined glucose concentration values. Shin describes “a display 214 that is used to display the calculated results of the raw glucose sensor data received via a download from the glucose monitor 100” and that can display other information including “trending information of the characteristic (e.g., rate of change of glucose), graphs of historical data, average characteristic levels (e.g., glucose),” among other things.

Ex-1008, ¶0062.

2. Claim 24: “The method of claim 23 wherein the in vivo portion of the transcutaneous glucose sensor comprises a substantially planar configuration.”

225. Shin discloses the method of claim 24.

226. Shin’s sensor has the claimed planar configuration. Ex-1008, FIG. 3:



3. Claim 25: “The method of claim 23 wherein the drift profile accounts for a break-in of the transcutaneous glucose sensor after the in vivo portion of the transcutaneous glucose sensor has been inserted into the body of the host.”

227. Claim 25 recites the term “a break-in.” The ’031 patent defines “break-in” broadly to include “electrochemical break-in,” “membrane break-in,” and “sensor break-in.” Further, “sensor break-in” encompasses both “electrochemical break-in” and “membrane break-in.” Ex-1001, 24:50-56, 28:25-30, 29:58-30:6. The patent explains that “sensor break-in” “refers without limitation to the time (after implantation) during which the sensor’s signal is becoming substantially representative of” glucose concentration, and that, “[i]n some embodiments, sensor break-in occurs prior to obtaining a meaningful calibration of the sensor output.” Ex-1001, 29:60-30:4.

228. Shin discloses the method of claim 25. Alternatively claim 25 would have been obvious.

229. Shin's drift profile—the valid sensitivity ranges—accounts for a break-in of the sensor as recited in claim 25, at least because Shin teaches using such ranges during time periods when break-in is occurring; thus the ranges, which reflect expected sensitivity changes over time, necessarily account for, or reasonably would have been understood as accounting for, sensitivity changes resulting from break-in.

230. In certain of Shin's embodiments, calibration begins after the glucose sensor is "initialized"/"stabilized." Ex-1008, ¶0066 ("After installation into the body, the glucose sensor 12 is initialized to achieve a steady state of operation before starting a calibration process."), ¶0068 ("After stabilization/initialization is complete the glucose monitor 100 is calibrated to accurately interpret readings from the newly installed glucose sensor 12."). Initialization is stated to take "an hour or less." Ex-1008, ¶0067; Ex-1008, ¶0068 ("[p]referably, stabilization is complete after 60 minutes"). Shin also describes embodiments that "omit the initialization/stabilization process" (Ex-1008, ¶0067) and where calibration begins following sensor insertion.

231. Thus Shin's method calibrates sensor data, using the drift profile discussed above, as soon as initialization is complete (Ex-1008, ¶0069) or

following sensor insertion and without an initialization period. In both embodiments, Shin's drift profile (the valid sensitivity ranges, which Shin teaches are predetermined based on how long the sensor has been use) accounts for "break-in" as recited in claim 25.¹¹

232. In Shin's embodiments where there is an initialization period before sensor data are calibrated, calibration begins when there is still "break-in" as recited claim 25; there is still "break-in" after the initialization period because "break-in" as recited in claim 25 includes more than just electrochemical break-in and can be on-going during and after a first calibration. Thus, Shin's drift profile (the valid sensitivity ranges), which is used for calibration after Shin's initialization but still when "break-in" as recited in claim 25 is occurring, necessarily accounts for, or reasonably would have been understood as accounting for, the sensitivity changes that are expected during such "break-in."

233. In Shin's embodiments where there is no initialization period and calibration begins following sensor insertion, Shin's drift profile necessarily accounts for, or reasonably would have been understood as accounting for, the

¹¹ I have been informed that a single embodiment meeting each and every claim element is sufficient to anticipate a patent claim, and thus either of Shin's embodiments alone is sufficient to anticipate claim 25.

sensitivity changes occurring during the break-in that was known to occur following sensor insertion. *See, e.g.*, Wilson (Ex-1023) at 21-22 (discussed above in ¶46).

234. Claim 25 alternatively would have been obvious in view of the POSA's knowledge that glucose sensors undergo break-in and the general desire to improve calibration methods. *E.g.*, Wilson (Ex-1023) at 21-22 (describing the "run-in" period of subcutaneously implanted glucose sensors); Lesperance (Ex-1018) at 183 (describing a conversion algorithm "that permits utilization of the CGMs monitor for glucose monitoring" during the first 12-24 hours after sensor insertion, when sensor sensitivity is particularly variable).¹² The POSA using valid

¹² In Lesperance, the authors sought to develop a conversion algorithm to make use of CGM data during the first 12-24 hours following sensor insertion, when "the sensor demonstrates glucose and time dependencies that preclude direct application of the company-provided conversion algorithm." Lesperance (Ex-1018) at 183. "That the CGMS sensors may demonstrate a drift in sensitivity over time and may have variable sensitivity as a function of glycemic levels does not necessarily preclude its use in research. In fact, the high initial sensitivity of the sensors led us to suggest that the CGMS may be useful for short-term monitoring, such as (continued...)"

sensitivity ranges that are based on expected sensitivity changes over time, as expressly taught in Shin, would have used valid sensitivity ranges that account for break-in, for time periods starting from sensor insertion and for time periods after the first hour of sensor wear (after Shin's initialization period, when break-in is still occurring), to improve sensor calibration and make use of sensor data during the initial hours following sensor insertion.

4. Claim 26: “The method of claim 23 wherein the drift profile accounts for a change in sensitivity over time of the in vivo portion of the transcutaneous glucose sensor to the glucose concentration within the body of the host.”

235. Shin discloses the method of claim 26.

236. *See* discussion of claim 23[c], in section X.B.1.d) (¶¶219-222).

required in oral glucose tolerance testing (OGTT). Here, we report on the results of a study designed to establish a sensor current-to-glucose conversion algorithm for the CGMS that may permit its use in the initial hours following sensor insertion and where wide swings in glucose levels were expected, such as with OGTT.”

Lesperance (Ex-1018) at 184.

5. Claim 27: “The method of claim 23 wherein the drift profile accounts for a change in baseline over time associated with the in vivo portion of the transcutaneous glucose sensor.”

237. Shin discloses the method of claim 27. Claim 27 also would have been obvious based on Shin and the POSA’s knowledge.

238. Shin’s drift profile—the valid sensitivity ranges disclosed in Ex-1008, ¶0103—accounts for a change in baseline over time. Shin teaches that calculation of the MSPSR accounts for a baseline shift (away from zero) and teaches comparing each calculated MSPSR to a valid sensitivity range to determine if the MSPSR is reasonable. Ex-1008, ¶¶0093-0103. Because each of Shin’s valid sensitivity ranges is used to determine whether the MSPSR (which includes a correction for a baseline change) is reasonable or not, each range accounts for baseline as well as sensitivity changes over time. Shin thus teaches that when the calculated MSPSR falls outside of a predetermined valid sensitivity range, there is an aberrant change in sensor sensitivity as well as baseline.

239. Specifically, Shin teaches that the MSPSR is calculated by the following method: first, an SPSR (sensitivity ratio) is calculated assuming 0,0 for baseline and using a single matched data pair; “[t]he slope of the line from the origin (0,0) and passing through the single paired calibration point 700 is the single-point sensitivity ratio (SPSR).” Ex-1008, ¶0088. However, if the SPSR “is less than a sensitivity threshold value, then a modified SPSR (MSPSR) is

calculated using an offset value included in a modified single-point calibration equation.” Ex-1008, ¶0093. In one embodiment, if the SPSR is less than 7, then “an offset value of 3 is used to calculate the MSPSR.” Ex-1008, ¶0093. *See also* Ex-1008, ¶¶0099-0102 (discussing other threshold values). Accordingly, in such embodiments, when the SPSR is below a certain threshold value (e.g., 7), the difference between the SPSR and the predetermined threshold value is due to a change in baseline—in other words, if the SPSR is below an expected threshold value, then the assumption that baseline is zero and of the calibration curve passing through the origin (0,0) no longer applies.¹³

240. Shin then teaches calculating a modified SPSR (the MSPSR), using an offset to account for this change in baseline (away from zero). It is this MSPSR that is then compared to the valid sensitivity ranges, as discussed in Ex-1008, ¶0103. Shin teaches that an MSPSR calculated at a particular point in time that is outside of the predetermined valid sensitivity range for that point in time means there is both an aberrant sensitivity change as well as an aberrant baseline change. Ex-1008, ¶0103.

¹³ The SPSR, which is in units of mg/dl per nano-amp (Ex-1008, ¶¶0088-0089), is the inverse of sensor sensitivity, which is in units of nA per mg/dl.

241. Because Shin teaches comparing the MSPSR (which includes a correction for a baseline shift away from zero) to the valid sensitivity range, it must be the case that the valid sensitivity range accounts for sensitivity as well as baseline, and that valid sensitivity ranges that depend on the duration of sensor use account for sensitivity changes as well as baseline changes over time. In other words, in arriving at the predetermined valid sensitivity ranges that are based on how long the sensor has been in use and that are to be used in the comparisons to the calculated MSPSRs, Shin has considered baseline shifts as well as sensitivity shifts in determining these ranges, because the MSPSR itself accounts for baseline as well as sensitivity.

242. Claim 27 also would have been obvious based on Shin and the knowledge in the art that baseline often shifts over time, during sensor wear, and based on the desire to improve calibration and better detect aberrant changes in sensitivity and baseline (*see* ¶122, above). The POSA would have found it obvious to compare a calculated or experimental baseline to a valid baseline range, in addition to comparing each calculated sensitivity ratio (Shin's MSPSR) to a valid sensitivity range as expressly disclosed in Shin. The valid baseline ranges, like Shin's expressly disclosed valid sensitivity ranges, would be determined in advance—the valid baseline ranges could be determined from the same sensor testing conducted to determine the valid sensitivity ranges. *See* Ex-1008, ¶0103.

Such a modification of Shin's method would require an algorithm modification but no additional testing, and thus the POSA would have reasonably expected success in making this modification.

6. **Claim 28: "The method of claim 23 wherein the drift profile accounts for a change in baseline over time associated with the in vivo portion of the transcutaneous glucose sensor and a change in sensitivity over time of the in vivo portion of the transcutaneous glucose sensor to the glucose concentration within the body of the host."**

243. Shin discloses the method of claim 28.

244. See discussion of claims 26 and 27, in sections X.B.4 (§§235-236) and X.B.5 (§§237-242).

7. **Claim 29: "The method of claim 23 wherein the shift over time is an elapsed time measured from the beginning of the sensor session."**

245. Shin discloses the method of claim 29.

246. Shin's valid sensitivity ranges (or drift profile) account for a shift over an elapsed time measured from the beginning of the sensor session. Shin explains that each MSPSR is compared to a valid sensitivity range during calibration. Ex-1008, ¶0103. Shin teaches embodiments where calibration begins after "initialization"/"stabilization," which is a time period of about one hour following sensor insertion (Ex-1008, §§0066-68) and also teaches embodiments that "omit the initialization/stabilization process" (Ex-1008, ¶0067). In the latter embodiments, calibration begins immediately following sensor insertion; the

beginning of calibration and the determination of glucose concentration values thus corresponds to the time of sensor insertion, i.e., the beginning of the sensor session. In these embodiments, the drift profile accounts for shifts in sensitivity from this time.

8. Claim 30: “The method of claim 23 wherein the shift over time is associated at least in part with a change in one or more physical properties of an environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

247. Shin discloses the method of claim 30, and in the alternative Shin renders claim 30 obvious.

248. In Shin, the expected sensitivity changes reflected in Shin’s valid sensitivity ranges are associated at least in part with a change in a physical property of the sensor’s in-vivo environment. As discussed above, the valid sensitivity ranges are based on how long the sensor has been in use. Shin’s valid sensitivity ranges that are based on the length of time the sensor has been in use necessarily account for, or would have been understood as accounting for, sensitivity changes associated at least in part with a change in the environment over time. Indeed, Shin recognizes that physical properties of the environment affect sensor sensitivity. Ex-1008, ¶0117 (teaching that parameters such as “temperature, pH, salinity, and the like” can be accounted for in the calibration equation), ¶0141 (teaching that the calibration equation can include variables to

account for “calibration effecting parameters, such as environment”). It was also well known that the in-vivo environment surrounding the sensor changes over time, and that such environmental changes affect sensor sensitivity over time. *See* ¶¶43-47 and ¶¶130-131 above.

249. Alternatively, the POSA would have found it obvious that Shin’s valid sensitivity ranges that depend on the length of time of sensor use account for shifts over time in sensor sensitivity that are associated with such environmental changes. As discussed previously, the POSA understood that the in-vivo environment surrounding the sensor changes over time, and that such environmental changes affect sensor sensitivity over time. *See* ¶¶43-47 and ¶¶130-131 above.

9. **Claim 31: “The method of claim 30 wherein the one or more physical properties of the environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host is associated with at least one of: trauma, wound healing, blockage of a surface of the transcutaneous glucose sensor, inflammation, blood clotting, or biofouling.”**

250. Shin discloses the method of claim 31, and in the alternative Shin renders claim 31 obvious.

251. Claim 31 enumerates causes for the changes in the environment surrounding the in-vivo portion of the sensor. At least some of these causes (e.g., wound healing, inflammation) were known to inevitably occur following insertion of the sensor into the host. *See* ¶¶130-131 above. For example, as discussed above,

Godek notes that the host inflammatory response to implanted biomaterials is “ubiquitous” and that “no materials or device designs reported to date completely attenuate” such response. Godek (Ex-1024) at 30, 42. Accordingly, the shift over time that is associated at least in part with a change in a physical property of the environment surrounding the in-vivo portion of the sensor (*see* claim 30) necessarily is a shift associated with at least one of trauma, wound healing, etc., as recited in claim 31.

252. Claim 31 alternatively would have been obvious, for the same reasons discussed above for claim 30. The POSA would have found it obvious that Shin’s pre-determined valid sensitivity ranges are associated at least in part with a change in a physical property of an environment surrounding the in-vivo portion of the sensor, wherein the physical property is associated with trauma, wound healing, blockage of a surface of the transcutaneous glucose sensor, inflammation, blood clotting, and/or biofouling.

10. Claim 32: “The method of claim 23 wherein the shift over time is associated at least in part with a physical property of the transcutaneous glucose sensor, wherein the physical property corresponds to a membrane of the in vivo portion of the transcutaneous glucose sensor.”

253. Shin discloses the method of claim 32, and in the alternative Shin renders claim 32 obvious.

254. As discussed below for claim 35[b], Shin discloses and/or renders obvious a membrane. The shift over time taught in Shin and discussed above would have been understood as being associated in part with “a physical property correspond[ing] to a membrane of the in vivo portion” of the sensor, as recited in claim 32. Shin’s drift profile (Shin’s valid sensitivity ranges determined from expected sensitivity changes over time) necessarily is associated with the causes of sensitivity changes that contributed to those expected sensitivity changes, including causes that are associated with the membrane. Such causes associated with the membrane include membrane biofouling. *See* ¶139 above (discussing membrane biofouling). Alternatively, the POSA would have found it obvious that the causes of sensitivity changes include causes associated with a sensor membrane; it was known that sensor membranes change over time (due to biofouling, for example), and that such membrane changes affect sensor sensitivity. *See* ¶¶44-47 and ¶139 above.

11. Claim 33: “The method of claim 23 wherein the shift over time is an elapsed time measured from the insertion of the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

255. Shin discloses the method of claim 33.

256. As discussed above for claim 29, Shin discloses embodiments where calibration begins following sensor insertion. In such embodiments, the shift in sensitivity over time (reflected in Shin’s valid sensitivity ranges) corresponds to an

elapsed time measured from sensor insertion, as discussed in section X.B.7 (¶¶245-246) (discussing claim 29).

12. Claim 34: “The method of claim 23 wherein the drift profile has a first slope associated with a first time and a second slope associated with a second time, wherein the first time is different from the second time, wherein the first slope is different from the second slope.”

257. Shin discloses the method of claim 34, and in the alternative Shin renders claim 34 obvious.

258. Shin’s valid sensitivity ranges differ based on the length of time the sensor has been in use (inserted into the host), and as discussed above, constitute “a drift profile” as recited in claim 23. Each sensitivity range comprises a range of sensitivities (i.e., a range of slopes¹⁴). For sensitivity ranges that differ over time as taught in Shin (Ex-1008, ¶0103), the sensitivities (slopes) within one range, for one

¹⁴ Shin teaches that the calibration factor is calculated using linear regression. Ex-1008, ¶¶0087-0088 (discussing linear regression to calculate the SPSR), ¶¶0093-0102 (similar method used for the MSPSR). When solving for the calibration factor using linear regression as in Shin, the sensitivity corresponds to the slope of the line. E.g., Koudelka-Hep (Ex-1021) at 63 (explaining the in-vivo sensitivity is determined from the slope). Thus, a range of sensitivities corresponds to a range of slopes.

time period, will comprise sensitivities that differ from the sensitivities (slopes) in one or more subsequent ranges (for subsequent time periods). Accordingly, the valid sensitivity ranges that differ over time (the drift profile) comprise a first sensitivity (slope) associated with a first time, and a second sensitivity (slope) associated with a second time, where the slopes and times differ from each other.

259. It alternatively would have been obvious for Shin's valid sensitivity ranges that are based on the length of time of sensor use to include ranges with different slopes, for different time periods, in view of the well-documented observation that sensor sensitivity changes over time. E.g., Frost (Ex-1029) at 633-634, 637-638; Wisniewski (Ex-1030) at 611-612; Wilson (Ex-1023) at 21-22. The valid sensitivity ranges are pre-determined, based on sensor testing, and the POSA would have expected such ranges to include ranges with different slopes, for different time periods.

13. Independent claim 35

a) 35[Pre]. "A sensor system comprising:"

260. To the extent the preamble is limiting, it is disclosed in Shin. Shin describes a glucose monitor system comprising a sensor to detect glucose concentration. E.g., Ex-1008, ¶0002, ¶0031-0032, ¶0054, FIGS. 1-2.

- b) 35[a]. “a transcutaneous glucose sensor comprising: an ex vivo portion configured to remain outside of a body of a host; and an in vivo portion configured to be implanted within the body of the host,”**

261. Shin discloses the element of claim 35[a].

262. *See* discussion of claim 23[a], in section X.B.1.b) (¶¶213-216).

- c) 35[b]. “wherein the in vivo portion comprises: an electrode; and a membrane disposed over at least a portion of the electrode, wherein the membrane comprises at least one enzyme;”**

263. Shin discloses the element of claim 35[b]. Alternatively, a glucose sensor with a membrane as claimed would have been obvious.

264. The in-vivo portion of Shin’s sensor comprises an electrode. As discussed above with reference to FIG. 2, the “electrodes 20 of the glucose sensor 12 terminat[e] in the user’s subcutaneous tissue.” Ex-1008, ¶0057.

265. Shin’s glucose sensor also comprises “an enzyme coating.” Ex-1008, ¶¶0064-0065. The POSA would have understood that such coating serves to immobilise the enzyme (such that the enzyme cannot diffuse away, resulting in enzyme loss), while allowing glucose and oxygen to diffuse into the coating such that glucose can undergo the reaction catalyzed by the enzyme—in other words, the POSA would have understood such “enzyme coating” to be a membrane comprising the enzyme. *See* note 7 above, describing the ’031 patent’s discussions of “membrane.”

266. Shin also incorporates by reference a disclosure of a membrane comprising an enzyme that is disposed over an in-vivo portion of the electrode. For example, Shin in ¶0057 incorporates by reference Application No. 29/101,218, entitled “Glucose Sensor,” which describes a glucose sensor comprising electrodes, where “the tips of one or more of the electrodes are covered with an enzyme.” Ex-1009 at 2. The application continues to explain that “the glucose sensor may be covered with one or more membranes. Alternative variations may use different combinations or types of metals, enzymes, substrates and/or more or less membranes.” Ex-1009 at 2, FIG 1.

267. A membrane as recited in claim 35[b] also would have been obvious, at least based on the knowledge in the art that using a membrane was the preferred technique for immobilising glucose oxidase in CGMs, including commercial CGMs. *See* discussion above in ¶¶151-154. Indeed, as of the 2008 priority date, commercial CGMs were described, without exception, as having a sensor with “an enzyme-containing membrane.” *See* ¶32 above.

d) 35[c]. “wherein the transcutaneous glucose sensor generates a signal associated with a glucose concentration within the body of the host;”

268. Shin discloses the element of claim 35[c].

269. In Shin, “the glucose monitor 100 measures a continuous electrical current signal (ISIG) generated by the glucose sensor 12 relative to a concentration of glucose present in the subcutaneous tissue of the user’s body.” Ex-1008, ¶0069.

e) 35[d]. “electronics configured to receive the signal from the transcutaneous glucose sensor,”

270. Shin discloses the element of claim 35[d].

271. Shin’s system comprises electronics configured to receive signals from the sensor. E.g., Ex-1008, ¶0015 (“The glucose sensor is electronically coupled to the glucose monitor to supply the glucose monitor data.”), ¶0058 (“The glucose monitor 100 generally includes the capability to record and store data as it is received from the glucose sensor 12”), ¶¶0059-62, FIGS. 1-2.

f) 35[e]. “wherein the electronics comprises a memory, wherein the memory stores information associated with an expected change over time in a relationship between the signal and the glucose concentration within the body of the host,”

272. Shin discloses the element of claim 35[e]. Electronics with memory that stores calibration information also would have been obvious.

273. Shin’s electronics comprises memory that stores information associated with an expected change over time in sensor sensitivity. Because sensitivity defines in part a relationship between sensor signal and the glucose concentration within the host’s body, this information also is associated with an expected change over time in such relationship.

274. Shin explains: the “apparatus for calibrating glucose monitor data includes a glucose monitor, glucose sensor, a blood glucose meter and a processor. The glucose monitor includes a glucose monitor memory for storing glucose monitor data. The glucose sensor is electronically coupled to the glucose monitor to supply the glucose monitor data.” Ex-1008, ¶0015; Ex-1008, ¶0058 (“The glucose monitor 100 generally includes the capability to record and store data as it is received from the glucose sensor 12”). Thus the glucose monitor comprises a memory.

275. Shin’s “electronics” also includes Shin’s data processor, which, in certain embodiments, includes the software for calibrating sensor data and thus includes the “memory” as recited in claim 35[e]. Ex-1008, ¶¶0059-0060. Whether the “memory” storing the “information” as recited in claim 35[e] is in Shin’s glucose monitor or is in Shin’s data processor, Shin’s “electronics” meets the limitations of claim 35.

276. Shin’s memory stores information associated with an expected change over time in sensor sensitivity. Ex-1008, ¶¶0087-0104. Shin teaches that the calibration factor (the MSPSR) is compared to “valid sensitivity ranges,” and such ranges can depend on “how long the sensor has been in use.” Ex-1008, ¶0103. Shin thus teaches embodiments where different valid sensitivity ranges are used, each range associated with a length of time of sensor use.

277. The different valid sensitivity ranges that depend on the length of time of sensor use are based on expected sensitivity changes associated with sensor use. Thus the valid sensitivity ranges constitute “information associated with an expected change over time in a relationship between signal and the glucose concentration within the body of the host,” as recited in claim 35[e]. *Compare* Ex-1008, ¶0103 to Ex-1001, 213:5-43, 213: 33-36 (.... In some embodiments, the a priori sensitivity information defines a range (e.g., within boundaries and/or guard bands) of acceptable change (increase and/or decrease) in sensitivity.”)), 216:44-61.

278. In addition, Shin’s valid sensitivity ranges must be stored in memory, because each calculated MSPSR is compared to a valid sensitivity range that has been predetermined and that therefore must be stored in the system. Indeed, Shin teaches that the example valid sensitivity range of 1.5 to 15 was determined in-vitro and thus prior to sensor insertion (Ex-1008, ¶0103), and so that range must be stored in system memory for the system to compare the MSPSR to it.

279. A system with electronics comprising memory storing information to be used in calibration also would have been obvious, at least because such electronics were a basic and essential component of CGMs. Say, for example, teaches systems with electronics that include memory (with calibration information). 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. Say (Ex-1011), 43:36-44, FIGS. 18A, 18B. *See also* Say (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”).

g) 35[f]. “wherein the electronics is configured to generate a glucose concentration value based at least in part on the signal and the information associated with the expected change over time in the relationship.”

280. Shin discloses the element of claim 35[f].

281. Shin’s system comprises electronics configured to calculate a glucose concentration value based at least in part on the sensor signal and the valid sensitivity ranges discussed above.

282. Shin explains that the glucose monitor (or the data processor) can contain the software to calibrate sensor signals and display a glucose concentration value. Ex-1008, ¶¶0060-0061. Thus, Shin’s electronics (which include the glucose monitor and the data processor) are configured to determine a glucose concentration value. Specifically, Shin explains:

The glucose monitor 100 takes raw glucose sensor data from the glucose sensor 12 and assesses it during real-time and/or stores it for later processing or downloading to the data processor 200, which in turn analyzes, displays, and logs the received data.... In alternative embodiments, the glucose monitor includes at least portions of the software described as contained within the data processor 200 above. The glucose monitor might contain the necessary software to calibrate glucose sensor signals, display a real-time blood glucose value, show blood glucose trends, activate alarms and the like.

Ex-1008, ¶¶0060-0061.

283. In addition, the electronics determine the glucose concentration value based at least in part on Shin's valid sensitivity ranges—i.e., on the expected change over time in the relationship as claimed. When processing sensor data and determining a glucose concentration value, Shin's system compares the MSPSR (Shin's calibration factor, which is calculated daily in preferred embodiments¹⁵) to a valid sensitivity range, where the range that is used in the comparison can depend on how long the sensor has been in use. "[T]he MSPSR is compared to a valid sensitivity range to determine if the newly calculated MSPSR is reasonable." Ex-1008, ¶0103. If the MSPSR on a particular day is outside of the valid sensitivity

¹⁵ Ex-1008, ¶0085; ¶0082 (explaining that a calibration factor is used to convert signal in nano-amps into "a blood glucose level (mg/dl or mmol/l)").

range for that day, then a calibration error alarm can notify the user of a potential problem. In this way—by comparing each MSPSR to a valid sensitivity range that depends on how long the sensor has been in use, to determine whether or not to accept that MSPSR and calibrate sensor data and generate a glucose concentration value—Shin’s system determines a glucose concentration value based at least in part on the information associated with the expected change in sensitivity, and thus in the relationship, over time.

- 14. Claim 36: “The sensor system of claim 35 wherein the change over time in the relationship is associated at least in part with a change in one or more physical properties of an environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host.”**

284. Shin discloses the sensor system of claim 36 and in the alternative renders claim 36 obvious.

285. *See* discussions of claims 30 and 35[e], in sections X.B.8 (§§247-249) and X.B.13.f) (§§272-279).

- 15. Claim 37: “The sensor system of claim 36, wherein the one or more physical properties of the environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host include trauma, wound healing, blockage of a surface of the transcutaneous glucose sensor, inflammation, blood clotting, or biofouling.”**

286. Shin discloses the sensor system of claim 37 and in the alternative renders claim 37 obvious.

287. *See* discussion of claim 31, in section X.B.9 (§§250-252).

16. Claim 38: “The sensor system of claim 35 wherein the change over time in the relationship is associated with the implantation of the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

288. Shin discloses the sensor system of claim 38.

289. As discussed above for claims 30 and 31, it was known that the host’s body reacts to sensor implantation, and that such reactions affect sensor sensitivity. Because Shin’s valid sensitivity ranges are predetermined, they are associated with the expected changes in sensor sensitivity that inevitably accompany sensor implantation. *See* ¶¶247-252 above.

17. Claim 39: “The sensor system of claim 35 wherein the change over time in the relationship is over an elapsed time measured from a beginning of a sensor session after implantation of the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

290. Shin discloses the sensor system of claim 39.

291. *See* discussion of claims 29 and 33, in sections X.B.7 (¶¶245-246) and X.B.11 (¶¶255-256).

18. Claim 40: “The sensor system of claim 35 wherein the change over time in the relationship is over an elapsed time measured from the implantation of the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

292. Shin discloses the sensor system of claim 40.

293. *See* discussion of claims 29 and 33, in sections X.B.7 (¶¶245-246) and X.B.11 (¶¶255-256).

- 19. Claim 41: “The sensor system of claim 35 wherein the change over time in the relationship is associated at least in part with a physical property of the transcutaneous glucose sensor, wherein the physical property of the transcutaneous glucose sensor corresponds to membrane of the in vivo portion of the transcutaneous glucose sensor.”**

294. Shin discloses the sensor system of claim 41 and in the alternative renders claim 41 obvious.

295. See discussion of claim 32, in section X.B.10 (¶¶253-254).

20. Independent claim 42

- a) 42[Pre]. “A method for monitoring a glucose concentration, the method comprising:”**

296. To the extent the preamble is limiting, it is disclosed in Shin. Shin describes a method for monitoring glucose concentration in a host. E.g., Ex-1008, ¶0054 (“In preferred embodiments of the present invention, the sensor and monitor are a glucose sensor and a glucose monitor for determining glucose levels in the blood and/or bodily fluids of a user.”).

- b) 42[a]. “beginning a sensor session associated with use of a transcutaneous glucose sensor, wherein the transcutaneous glucose sensor comprises: an ex vivo portion configured to remain outside of a body of a host; and an in vivo portion configured to be inserted within the body of the host;”**

297. Shin discloses the element of claim 42[a].

298. Shin discloses beginning a sensor session with use of a transcutaneous glucose sensor, as described in claim 42[a]. *See* discussion of claim 23[a], in section X.B.1.b) (§§213-216).

c) 42[b]. “wherein the transcutaneous glucose sensor is configured to generate a signal;”

299. Shin discloses the element of claim 42[b].

300. *See* discussions of claims 23[b] and 35[c], in sections X.B.1.c) (§§217-218) and X.B.13.d) (§§268-269).

d) 42[c]. “calibrating the transcutaneous glucose sensor by applying a priori information, wherein the a priori information comprises an expected relationship between the signal and a glucose concentration existing within the body of the host, wherein the relationship changes as a function of time;”

301. Shin discloses the element of claim 42[c].

302. Shin teaches calibrating the sensor by applying a priori information comprising expected sensitivity changes over time, as discussed previously. Sensitivity defines in part the relationship between signal and glucose concentration, and thus expected sensitivity defines in part the expected relationship between sensor signal and glucose concentration. In Shin, the a priori information (Shin’s valid sensitivity ranges) comprises expected sensitivity changes over time and thus also comprises an expected relationship (between signal and glucose concentration) that changes over time, as recited in claim 42[c].

303. Shin teaches that each calculated MSPSR is compared to a pre-determined valid sensitivity range, and that the valid sensitivity ranges used over time can be ranges that depend on how long the sensor has been in use. Ex-1008, ¶0103. As a result of this comparison, the system either accepts or rejects the MSPSR, and if the MSPSR is accepted sensor calibration proceeds. In this way, Shin discloses calibrating the sensor “by applying a priori information” (the pre-determined valid sensitivity ranges) comprising “an expected relationship between the signal and a glucose concentration existing within the body of the host, wherein the relationship changes as a function of time,” as recited in 42[c]. *See also* discussions of claims 23[c] and 35[f], in sections X.B.1.d) (¶¶219-222) and X.B.13.g) (¶¶280-283).

e) 42[d]. “generating a glucose concentration value based at least in part on the calibrating; and”

304. Shin discloses the element of claim 42[d].

305. *See* discussions of claims 23[c] and 35[f], in sections X.B.1.d) (¶¶219-222) and X.B.13.g) (¶¶280-283).

f) 42[e]. “displaying the glucose concentration value.”

306. Shin discloses the element of claim 42[e].

307. *See* discussion of claim 23[d], in section X.B.1.e) (¶¶223-224).

21. Claim 43: “The method of claim 42 wherein the time the relationship changes is an elapsed time measured from the beginning of the sensor session.”

308. Shin discloses the method of claim 43.

309. *See* discussion of claim 29, in section X.B.7 (¶¶245-246).

22. Claim 44: “The method of claim 42 wherein the time the relationship changes as a function of time is associated at least in part with a change in one or more physical properties of an environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host.”

310. Shin discloses the method of claim 44 and in the alternative renders claim 44 obvious.

311. *See* discussion of claim 30, in section X.B.8 (¶¶247-249).

23. Claim 45: “The method of claim 44 wherein the one or more physical properties of the environment surrounding the in vivo portion of the transcutaneous glucose sensor within the body of the host include trauma, wound healing, blockage of a surface of the transcutaneous glucose sensor, inflammation, blood clotting, or biofouling.”

312. Shin discloses the method of claim 45 and in the alternative renders claim 45 obvious.

313. *See* discussion of claim 31, in section X.B.9 (¶¶250-252).

- 24. Claim 46: “The method of claim 42 wherein the time the relationship changes as a function of time is associated at least in part with a physical property of the transcutaneous glucose sensor, wherein the physical property of the transcutaneous glucose sensor corresponds to a membrane of the in vivo portion of the transcutaneous glucose sensor.”**

314. Shin discloses the method of claim 46 and in the alternative renders claim 46 obvious.

315. See discussion of claim 32, in section X.B.10 (¶¶253-254).

XI. AVAILABILITY FOR CROSS-EXAMINATION

316. 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

317. 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

318. 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: May 10, 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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