

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TERUMO BCT INC.,

Petitioner

v.

HAEMONETICS CORP.,

Patent Owner

IPR2025- 01420

U.S. Patent No. 10,792,416

**DECLARATION OF GARY D. FLETCHER, PH.D. IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO.
10,792,416**

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EXHIBIT LIST

Exhibit	Reference
1001	U.S. Patent No. 10,792,416 (“’416 patent”)
1002	File History of the ’416 patent
1004	U.S. Patent No. 4,898,675 (“Lavender”)
1005	“Calculations in Apheresis” (“Neyrinck”)
1006	U.S. Patent Publication No. 2002/0033370 (“Bainbridge”)
1007	U.S. Patent Publication No. 2011/0097344 (“Darashkevich”)
1008	U.S. Patent No. 8,075,468 (“Min”)
1009	U.S. Patent Publication No. 2017/0029762 (“Turgut”)
1010	U.S. Patent No. 6,296,602 (“Headley”)
1011	U.S. Patent No. 9,370,324 (“Barrett”)
1012	“Membrane versus centrifuge-based therapeutic plasma exchange: a randomized prospective crossover study,” Carsten Hafer et al., <i>Int. Urol. Nephrol</i> (2016) 48:133-138; Springer Science+Business Media Dordrecht 2015.
1013	“Volume Limits – Automated Collection of Source Plasma,” November 4, 1992, Memorandum issued by the FDA Center for Biologics Evaluation and Research, Docket Number FDA-2013-S-0613.
1014	Bruce C. McLeod, MD, et al., “Apheresis: Principles and Practice,” 3rd Edition, AABB Press 2010.
1015	Sergent SR, Ashurst JV. Plasmapheresis. [Updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560566/?report=printable
1016	Japanese Patent Publication No. JP 2002-282352 A and certified Japanese to English translation (“Takagi”)
1017	J. Klespitz and L. Kovács, “Identification and control of peristaltic pumps in hemodialysis machines,” 14th IEEE International Symposium on Computational Intelligence and Informatics 83-87 (2013)
1018	Curriculum Vitae (“CV”) of Dr. Gary D. Fletcher

I. INTRODUCTION

1. I, Dr. Gary D. Fletcher, Ph.D., of Media, Pennsylvania, declare that:

2. I have been retained as a technical expert by counsel on behalf of Terumo BCT, Inc. (“Petitioner”). I understand that Petitioner is requesting that the Patent Trial and Appeal Board institute an *Inter Partes* review (“IPR”) proceeding of U.S. Patent No. 10,792,416 (“’416 patent”).

3. I have been asked by Petitioner’s counsel (“Counsel”) to provide my independent analysis and consideration of whether certain references teach or suggest the features recited in claims 1–30 (the “challenged claims”) of the ’416 patent. My opinions and the bases for my opinions are set forth below. My opinions are based on my education and experience.

4. In writing this Declaration, I have considered the following: my own knowledge and experience, including my teaching and work experience in the fields of blood sample collection and analysis, plasma apheresis equipment, and related technology; and my experience of working with others involved in those fields.

5. I am not, and never have been, an employee of Petitioner. I have no financial interest in either party or in the outcome of this proceeding. I am being compensated for my work as an expert on an hourly basis, for all tasks involved. My compensation is not dependent on the outcome of these proceedings or on the content

of my opinions. I will not receive any added compensation based on the outcome of any IPR or other proceeding involving the '416 patent.

II. QUALIFICATIONS

6. My qualifications for forming the opinions in this report are summarized here and explained in more detail in my curriculum vitae ("CV"), which is provided as EX1018 appended hereto.

7. As detailed in my CV, I have extensive experience in the design, development, and manufacture of medical devices including blood processing technologies, with a career spanning over 30 years in this field. I have specific expertise in the design and development of blood fractionation technologies and have a sound understanding of the relevant technology and techniques used to separate plasma from a donor's blood.

8. I am Founder and Principal Consultant at RnDDx Solutions LLC, a consulting firm founded in 2015, focused on industrial mechanical engineering, and research and product development, in medical devices, blood separation devices, point-of-care blood sample testing, diagnostics, optical devices, and on providing expert witness services, *e.g.*, for patent litigation, including subject matter expertise in medical device engineering, and subject matter expertise in medical devices for blood collection and blood sample processing for diagnostics

and therapeutics. I have particular expertise in mechanical engineering design and development of blood collection and stabilization systems, blood separation, and blood and cell preparation for both diagnostic and therapeutic applications. I have expertise in the development of blood separation devices, and have served as a consultant advisor to medical device companies developing blood separation devices. A complete list of my patents, publications, professional activities, and honors that I have received is set forth in my curriculum vitae, attached hereto as EX1018.

9. I am also co-Founder of a startup biotech company, Raven Biomaterials, developing novel patented immunomagnetic blood cell separation technology, with both diagnostic and cell therapy manufacturing applications.

10. I received my Bachelor of Arts in Physics and Mathematics from DePauw University, Greencastle, Indiana, in 1976, my Master of Philosophy degree in Physics from Yale University in 1978, and my Doctor of Philosophy degree in Physics, also from Yale University, in 1983. My doctoral research was in experimental atomic physics, where I gained experience in mechanical, electrical, and software engineering, optical physics, and vacuum engineering, developing and maintaining the experimental apparatus used in my research. I conducted postdoctoral research in experimental atomic and laser physics as a Postdoctoral Research Associate in Physics and Assistant Professor of Physics at the University

of Virginia. At Lawrence Livermore National Laboratory I expanded my expertise in mechanical and optical engineering by developing x-ray spectroscopic and imaging instruments to measure x-rays emitted from laser-produced high-temperature plasmas. I have 23 years of senior industrial executive experience building new products and new businesses in the healthcare, life sciences, material sciences, medical device, imaging, and diagnostics space. That experience includes leading R&D and product development engineering teams of mechanical, electrical, optical, and software engineers. Among the positions described in my curriculum vitae, my industry experience includes engineering leadership role in 1996 in a company attempting to develop a noninvasive glucose measurement sensor. From 1996 to 2001, I led Engineering and Advanced Technology, including teams of optical, mechanical, electrical, software imaging, and clinical laboratory engineers, developing a noninvasive human complete blood count diagnostic device and diagnostic blood perfusion assessment tool, for a medical diagnostic startup company. As technical manager at Sarnoff Corporation from 2001 – 2004 I led a team developing and licensing a painless minimally invasive blood glucose monitor.

11. As an R&D director at Becton Dickinson (“BD”) from 2004 to 2014, I developed blood collection and blood separation devices for diagnostic testing. I led a 5-member technology development group executing technology strategy to

support medical device blood specimen collection and preservation business. I led research and development resolving manufacturing problems in core plastic blood collection products, and initiated a technology development stage-gate process to reduce technology risk in new product development. I also completed a “deep dive” technology assessment in blood fractionation technologies, leveraging and contacting academic experts in materials and fluidics, and led development effort assessing primary blood separation technologies. I also led product development in new business spaces, including the point of care blood collection and diagnostic testing space.

12. I have experience with the U.S. Patent system. I am co-inventor on fifteen issued U.S. Patents and ten issued European patents for devices and methods in the area of blood collection and processing including lancing devices and blood separation for diagnostic testing. A complete list of my patents is set forth in my curriculum vitae, attached hereto as EX1018.

13. Based on my experience and education, I believe that I am qualified to opine as to the knowledge and level of skill of one of ordinary skill in the art (“POSITA”; refer to §VI, below) at the time of the alleged invention of the ’416 Patent and what such a person would have understood at that time, and the state of the art during that time. Based on my experiences, I understand and know of the capabilities of persons of ordinary skill in this field during the mid-2010s to the

early 2020s and specifically during the time before the time of the alleged invention of the '416 Patent. Indeed, I worked closely with many such persons in the medical device and blood processing field during that time frame.

III. MATERIALS AND OTHER INFORMATION CONSIDERED

14. All of the opinions contained in this declaration are based on the documents I have reviewed and my professional judgment, as well as my education, experience, and professional knowledge. I am not an attorney and I am not offering any legal opinions in this declaration.

15. In forming the opinions expressed in this declaration, I relied upon my education, knowledge, and experience in the relevant field of the art, and have considered the viewpoint of a POSITA as of May 30, 2017, which I have been informed is the earliest effective filing date of the claims for purposes of this analysis. I have considered the materials referenced herein, including the '416 Patent (EX1001), the prosecution history (EX1002) of the '416 Patent, and the following materials:

- U.S. Patent No. 4,898,675, issued February 6, 1990 (“Lavender,” EX1004);
- “Calculations in Apheresis,” *Journal of Clinical Apheresis* 30:38–42 (2015) (“Neyrinck,” EX1005);

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- U.S. Patent Publication No. 2002/0033370, published March 21, 2002 (“Bainbridge,” EX1006);
- U.S. Patent Publication No. 2011/0097344, published April 28, 2011 (“Darashkevich,” EX1007);
- U.S. Patent No. 8,075,468, issued December 13, 2011 (“Min,” EX1008);
- U.S. Patent Publication No. 2017/0029762, published February 2, 2017 (“Turgut,” EX1009);
- U.S. Patent No. 6,296,602, issued October 2, 2001 (“Headley,” EX1010);
- U.S. Patent No. 9,370,324, issued June 21, 2016 (“Barrett,” EX1011);
- “Membrane versus centrifuge-based therapeutic plasma exchange: a randomized prospective crossover study,” Carsten Hafer et al., *Int. Urol. Nephrol* (2016) 48:133-138; Springer Science+Business Media Dordrecht 2015. (EX1012);
- “Volume Limits – Automated Collection of Source Plasma,” November 4, 1992, Memorandum issued by the FDA Center for Biologics Evaluation and Research, Docket Number FDA-2013-S-0613. (EX1013);
- Bruce C. McLeod, MD, et al., “Apheresis: Principles and Practice,” 3rd Edition, AABB Press 2010. (EX1014);

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- In: Sergent SR, Ashurst JV. Plasmapheresis. [Updated 2023 Jul 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from:
<https://www.ncbi.nlm.nih.gov/books/NBK560566/?report=printable>
(EX1015); and
- Japanese Patent Publication No. JP 2002-282352 A and English translation (“Takagi,” EX1016)
- J. Klespitz and L. Kovács, “Identification and control of peristaltic pumps in hemodialysis machines,” 14th IEEE International Symposium on Computational Intelligence and Informatics 83-87 (2013) (EX1017).

16. I have considered these materials through the lens of a POSITA, which is discussed further in §§V and VI (below) related to the ’416 Patent as of the effective filing date, and I have done so during my review of these materials.

IV. SUMMARY OF MY OPINIONS

17. This Declaration explains the conclusions that I have formed based on my knowledge and experience and my review of the references (prior art) listed above. To summarize, I have concluded that:

- Claims 1, 7, 9, 11, 14, and 15 are obvious over Lavender in view of Neyrinck;

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- Claims 2-6, 17-22, 24, 26, 28, and 29 are obvious over Lavender in view of Neyrinck, and Bainbridge;
- Claim 8 is obvious over Lavender in view of Neyrinck, and Darashkevich;
- Claim 23 is obvious over Lavender in view of Neyrinck, Bainbridge, and Darashkevich;
- Claims 10 and 13 are obvious over Lavender in view of Neyrinck, and Min;
- Claim 25 is obvious over Lavender in view of Neyrinck, Bainbridge, and Min;
- Claim 12 is obvious over Lavender in view of Neyrinck, Min, and Turgut;
- Claim 27 is obvious over Lavender in view of Neyrinck, Bainbridge, Min, and Turgut; and
- Claims 16 and 30 are obvious over Lavender in view of Neyrinck, Bainbridge, Headley, and Barrett.

V. LEGAL PRINCIPLES

18. In forming my analysis and conclusions expressed in this declaration, I have applied the legal principles described in the following paragraphs, which were provided to me by Terumo's counsel.

A. Claim Construction

19. I understand that a claim must be construed under the *Phillips* standard. Under that standard, words of a claim are given their plain and ordinary meaning as understood by a POSITA at the time of invention, in light of the specification and prosecution history, unless those sources show an intent to depart from such meaning, as well as pertinent evidence extrinsic to the patent. For purposes of this declaration, I applied the plain and ordinary meaning of each term as would have been understood by a person of ordinary skill in art at the time of the alleged invention unless explicitly stated otherwise.

B. Anticipation

20. I understand that a patent claim is invalid if it is anticipated by a single item of prior art. I understand that an anticipation analysis involves two steps. First, the patent claims are construed to ascertain their scope. Second, each construed asserted claim is compared to the prior art reference on an element-by-element basis. If the prior art reference discloses or contains each and every element of the claimed invention, either expressly or inherently, then it anticipates the claim.

21. I understand that anticipation by inherent disclosure is appropriate only when a prior art reference necessarily includes or discloses the unstated claim element. I also understand that the discovery of a new or previously unreported or unappreciated property of a prior art composition, or of a scientific explanation for how a prior art composition operates, does not make the prior art composition patentably new to the entity or person that discovered the new property or mode of operation. I further understand that there is no requirement that a POSITA would have recognized the inherent disclosure at the time of the invention.

22. For anticipation by a prior art publication or document, I understand that the reference's description must enable a POSITA to practice the claimed invention without undue experimentation. I further understand that the following factors may be considered to determine whether any experimentation would have been undue:

- A) The quantity of experimentation necessary;
- B) The amount of direction or guidance presented;
- C) The presence or absence of working examples;
- D) The nature of the claimed invention;
- E) The state of the prior art;
- F) The relative skill of those in the art;
- G) The predictability or unpredictability of the art; and

H) The breadth of the claims.

C. Obviousness

23. I understand that a patent claim can be considered to have been obvious to a POSITA at the time the application was filed. This means that, even if all of the elements of a claim are not found in a single prior art reference, the claim is not patentable if 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 the application was filed.

24. I further understand that a determination of whether a claim would have been obvious must consider several factors, including, among others: (i) the level of ordinary skill in the art at the time the application was filed; (ii) the scope and content of the prior art; and (iii) what differences, if any, existed between the claimed invention and the prior art.

25. I understand that the teachings of two or more references may be combined in the same way as disclosed in the claims, if such a combination would have been obvious to a person of ordinary skill in the art. In determining whether a combination based on either a single reference or multiple references would have been obvious, it is appropriate to consider at least the following factors:

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- a. whether the teachings of the prior art references disclose known concepts combined in familiar ways, which, when combined, would yield predictable results;
- b. whether a POSITA could implement a predictable variation, and would see the benefit of doing so;
- c. whether the claimed elements represent one of a limited number of known design choices, and would have a reasonable expectation of success by a POSITA;
- d. whether a POSITA would have recognized a reason to combine known elements in the manner described in the claim;
- e. whether there is some teaching or suggestion in the prior art to make the modification or combination of elements claimed in the patent; and
- f. whether the innovation applies a known technique that had been used to improve a similar device or method in a similar way.

26. I understand that a POSITA has ordinary creativity and is not an automaton.

27. I understand that in considering obviousness, it is important not to determine obviousness using the benefit of hindsight derived from the patent being considered, and I have not done that in regards to my opinions expressed herein.

28. I understand that certain factors—often called “secondary considerations”—may support or rebut an assertion of obviousness of a claim. I understand that such secondary considerations include, among other things, commercial success of the alleged invention, skepticism of those having ordinary skill in the art at the time of the alleged invention, unexpected results of the alleged invention, any long-felt but unsolved need in the art that was satisfied by the alleged invention, the failure of others to make the alleged invention, praise of the alleged invention by those having ordinary skill in the art, and copying of the alleged invention by others in the field. I further understand that there must be a nexus—a connection—between any such secondary considerations and the alleged invention. I also understand that contemporaneous and independent invention by others is a secondary consideration tending to show obviousness.

VI. Level Of Ordinary Skill

29. In my opinion, a POSITA would have had, as of what I understand to be the earliest claimed filing date of May 30, 2017, a bachelor’s degree in biomedical engineering, or a related field, such as physical sciences, physics, computer engineering, electrical engineering, or the like, and a minimum of two to three years

of experience related to blood separation devices or blood processing devices. A higher level of education or specific skill might make up for less experience, and vice versa.

VII. Background on Plasma Apheresis

30. The '416 patent relates to apheresis systems, specifically apparatuses and methods for plasmapheresis, which is also called plasma apheresis—the extracorporeal separation and collection of plasma from whole blood, with cellular components returned to the donor.

31. Plasmapheresis, also known as plasma exchange or therapeutic plasma exchange, has been a clinical procedure since the 1960s. EX1014, Chapter 1: Development of Apheresis Instrumentation. It selectively removes plasma and returns cellular components along with replacement fluid using centrifugation or membrane filtration. EX1015. The earliest methodologies emerged from continuous centrifugation techniques in the 1960s, evolving to membrane-based and automated extraction systems. Early systems typically required large volumes of anticoagulants, continuous supervision by trained personnel, and bulky, non-portable equipment. Over time, manufacturers have introduced increasingly sophisticated machines that automate component separation, enhance flow control, monitor patient safety, and optimize plasma yield.

32. In therapeutic plasmapheresis, plasma containing pathogenic substances (such as autoantibodies or toxins) is removed and replaced with a substitution fluid (*e.g.*, saline, albumin, or donor plasma). In donor plasmapheresis, the plasma itself is collected for use in transfusion or further fractionation, and the remaining blood components (*e.g.*, red blood cells, white blood cells, platelets) are reinfused into the donor.

33. In automated plasmapheresis, whole blood is drawn from the donor, mixed at a specified ratio with anticoagulant, and then separated into anticoagulated plasma and red blood cells and other cellular components. Once a target volume of anticoagulated plasma has been collected, the withdrawal of whole blood from the donor ceases, and the red blood cells and other cellular components are returned to the donor. EX1014, Chapter 4: Current Instrumentation of Apheresis.

34. The FDA issued guidelines for registered blood collection centers as to the volume of plasma that may be collected during plasmapheresis in order to improve the consistency of procedures for manufacturing source plasma, and to minimize the opportunity for staff error. EX1013. The FDA Memo noted inconsistencies due to the various types of anticoagulant solutions used, differing concentrations of the anticoagulant, and the range of anticoagulant to plasma ratios. The FDA Memo set forth a simplified plasma volume nomogram, in which the volume (or weight) of plasma that may be collected from a particular donor is limited

to ensure donor safety and comfort. The FDA nomogram limits the volume (or weight) of plasma based on the weight of the donor, and establishes the volume of anticoagulant that may be added to a 1:16 ratio of anticoagulant to anticoagulated blood, or 0.06 parts anticoagulant to 1 part anticoagulated blood, to determine a maximum collection volume for the total of the plasma plus the anticoagulant for a particular donor. EX1013.

35. At the time the '416 patent was filed, apheresis optimization techniques were well known in the art and routinely employed to improve donor safety, maximize plasma yield, and increase procedural efficiency. Clinicians and device manufacturers commonly utilized formulas based on donor-specific parameters—such as weight, height, body mass index, sex, and hematocrit—to estimate total blood volume and determine safe and effective plasma collection volumes. EX1014, p. 52 (“Some instruments limit both dose rate and total citrate infused based on an estimate of subject blood volume calculated from sex, height, and weight,” p. 55, “Nomograms based on height, weight, and hematocrit are used to predict the consequences of volume removal [of plasma],” p. 99, “Flow rates are controlled by donor-specific data entered,” and Table 6-8 on p. 135, showing maximum plasma collection volumes based on donor sex and weight.) Plasmapheresis systems often incorporated fixed anticoagulant-to-anticoagulated-blood ratios (ACRs), typically between 1:8 and 1:16, and adjusted fluid flow rates

accordingly to maintain proper anticoagulation while minimizing citrate-related adverse effects. EX1014, p. 129 (Table 6-3). Furthermore, advanced plasmapheresis systems used real-time sensor feedback (*e.g.*, pressure, volume, optical detection) to dynamically monitor draw and return cycles¹, enabling adjustments to target volumes during the procedure.² Iterative recalculations of collection targets, particularly in multi-cycle procedures, were also recognized as necessary due to progressive changes in hematocrit and plasma composition. As such, individualized plasma volume estimation, anticoagulant adjustment, and cycle-by-cycle recalibration were part of the established technical knowledge in the field prior to the filing of the '416 patent. *See, e.g.*, EX1016.

VIII. '416 Patent Overview

A. The '416 Patent is Related to Plasma Apheresis

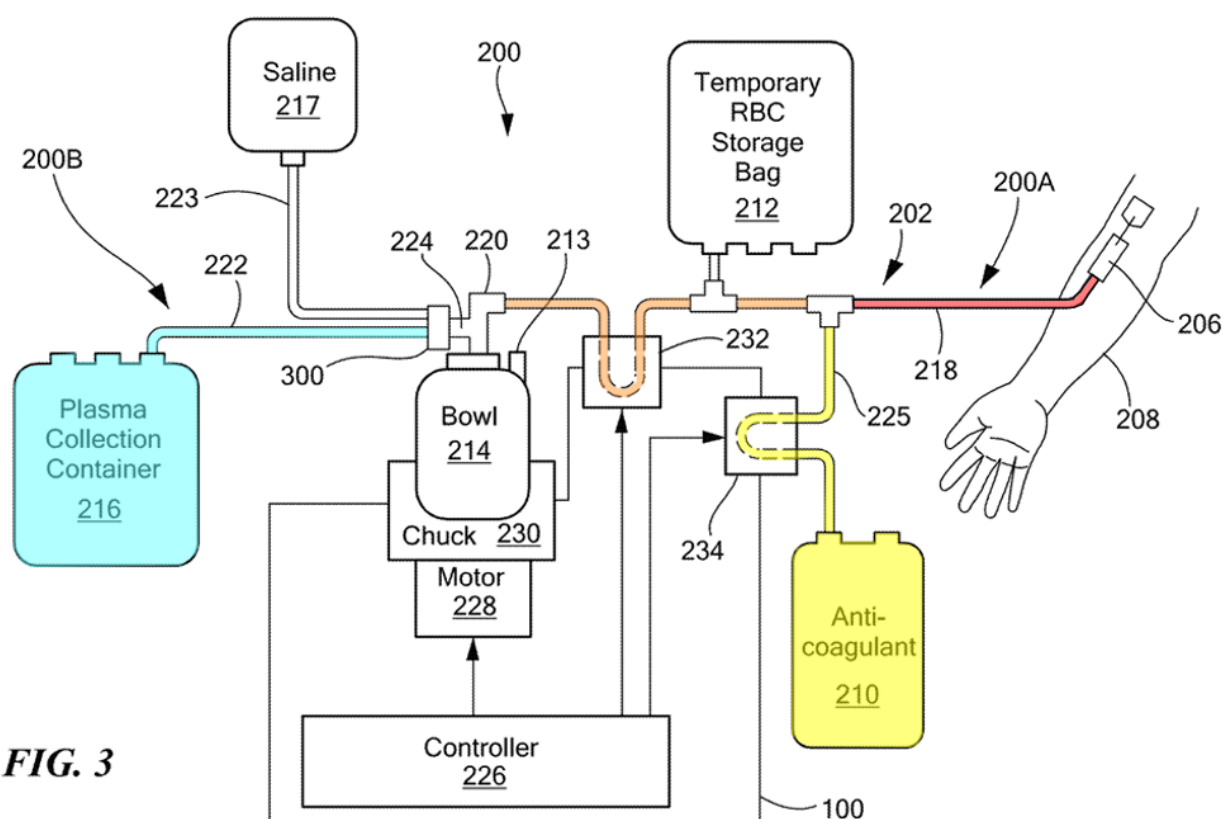
36. The '416 patent, which I understand issued on October 6, 2020, relates to a “system and method for collecting plasma” in blood apheresis systems. EX1001, Title, 1:13-15. “Apheresis is a procedure in which individual blood components,”

¹ *See* EX1014, p. 14, “Celltrifuge II [a blood-processing centrifuge] included an optical sensor for monitoring the collected product and automatically adjusting the pump speeds to maintain efficient separation without constant operator attention”; p. 78, “All reservoirs are monitored by electronic scales, and when specified maximum weights are reached, the instrument automatically switches from draw phase to return phase.”

² *See, e.g.*, EX1014, p. 14, “The pump flow rates—and, thereby, the component collection—are controlled by the microprocessor in response to the optical monitor.”

e.g., plasma and red blood cells, “can be separated and collected from whole blood.”

EX1001, 1:18-20. The '416 patent specifically relates to plasma apheresis, which is plasma collection. Figure 3 of the '416 patent shows one embodiment of a plasma apheresis system.



EX1001, Fig. 3 (annotated).

37. Plasma apheresis involves withdrawing whole blood from a donor using venous access device 206. EX1001, 7:62-65. Pump 232 “causes the whole blood to be drawn from the donor” through an inlet line 218 (red) and pump 234 adds a fixed amount of anticoagulant “into the whole blood” through “[a]n anticoagulant line” 225 (yellow) connected “to the inlet line.” EX1001, 8:60-65, 9:1-

7. Anticoagulant is introduced in fixed proportions to the whole blood drawn from the donor to prevent blood clotting in the draw line. *See* EX1013. “[T]he anticoagulant mixes with the plasma component” because “the osmolarity of the red blood cells prevents the anticoagulant . . . from entering/remaining with the red blood cells.” EX1001, 10:25-28.

38. Then, the mixture (orange) of anticoagulant and “withdrawn whole blood . . . enters a blood component separation device,” *e.g.*, centrifuge bowl 214, which “separates the whole blood into its constituent components,” *e.g.*, “plasma, platelets, red blood cells (“RBCs”) . . . [and] white blood cells.” EX1001, 7:32-7:43, 9:17-27. The donor’s plasma, *i.e.*, pure plasma, with anticoagulant introduced during the collection process, exits the blood component separation device and is collected and stored in a collection container (*e.g.*, a bag, in blue above). EX1001, 4:5-12, 7:62-8:6. The anticoagulant and pure plasma combination is known as anticoagulated plasma or plasma product. EX1001, 12:39-40.

39. The FDA established guidelines regarding how much plasma any individual donor can donate. *See* EX1013. These guidelines consider donor parameters, like weight, hematocrit, and sex. *See* EX1013.

B. The ’416 Patent’s Purported Invention

40. The ’416 patent purports to solve problems associated with “determin[ing] the total volume of plasma that has been collected” from a donor

after the withdrawn whole blood is mixed with anticoagulant by tailoring the volume of plasma collected based on the donor's plasma volume and a target percentage of plasma to collect, and considering a donor's hematocrit level and the amount of anticoagulant added into the system. EX1001, 1:44-50, 1:60-2:18, 6:54-67.

41. Each donor has a different hematocrit level, which affects the amount of plasma in the donor's whole blood. EX1001, 10:37-39. The differing levels of hematocrit affect the volume of anticoagulant in a plasma collection bag ("anticoagulant volume"). EX1001, 10:46-49. Given this variability, the '416 patent discloses that controller 226 may determine the donor's plasma volume based on hematocrit and then calculate the target volume of plasma to collect. EX1001, 13:43-46. Controller 226 may also use the % AC equation below, which includes a predetermined ratio of anticoagulant to anticoagulated whole-blood and the donor's hematocrit to calculate the percentage of anticoagulant in the plasma container. EX1001, 10:58-11:28. In % AC equation below, "AC" is the inverse of the predetermined ratio of anticoagulant per unit of anticoagulated whole blood (*e.g.*, "AC" would be 16 if the ratio of anticoagulant to anticoagulated whole blood was 1:16) and Hct_D is the donor's hematocrit. EX1001, 10:58-11:28. Anticoagulated whole blood is extracted blood mixed with anticoagulant.

$$\% AC = \frac{1}{1 + (AC - 1)(1 - Hct_D)}$$

42. The '416 patent discloses that the controller also monitors the weight of the collection container using a weight sensor and uses it to determine the total volume of liquid in the collection container. EX1001, 9:64-66, 10:32-36. The controller uses the total volume of liquid in the collection container to calculate the volume of anticoagulant and pure plasma in the collection container. EX1001, 10:50-11:46. The '416 patent first calculates the anticoagulant volume. EX1001, 11:29-46. It then calculates the volume of pure plasma in the collection container by subtracting the anticoagulant volume from the total volume of liquid in the collection container. EX1001, 11:29-46.

43. The '416 patent also discloses two alternative methods of determining the amount of anticoagulant in the collection bag that do not consider a donor's hematocrit. These include determining the anticoagulant in the collection bag by: (i) monitoring the volume of anticoagulant added to the system based on the number of rotations of the anticoagulant pump, and (ii) measuring the change in weight of the anticoagulant container. EX1001, 11:11-46. Something to note is that "[b]ecause the osmolarity of the red blood cells prevents the anticoagulant from mixing with it, essentially all of the anticoagulant exits the bowl 214 and is collected within the

plasma collection container 216 along with the plasma.” EX1001, 10:67-11:4. Under this assumption, subtracting the volume of anticoagulant added to the system from the total volume in the collection container provides an estimate of the volume of pure plasma within the collection container. EX1001 at 10:67-11:4, 12:7-22. In both these methods disclosed in the ’416 patent, the volume of anticoagulant that is added is then used to calculate the volume of pure plasma collected in the plasma collection container by subtracting the added anticoagulant volume from the total volume in the collection container. EX1001, 10:67-11:4, 11:11-28, 12:7-22.

44. Of the three methods I discussed above, only the first, which is based on the predetermined ratio of anticoagulant to anticoagulated whole blood, considers the donor’s hematocrit. That method does not, however, use an amount of anticoagulant collected within the plasma collection container or supplied to the system to determine a percentage of anticoagulant within the collected plasma. EX1001, 12:50-54.

45. In the ’416 patent, each method to determine the volume of pure plasma is repeated “until a target volume of pure plasma is collected in the plasma collection container,” *e.g.*, the volume the volume determined by calculating “the total volume of plasma to collect on the individual donor (*e.g.*, based on their height, weight, hematocrit, blood volume and/or plasma volume).” EX1001, 12:61-65. When the system reaches a target volume of pure plasma, the controller “stops the draw of

whole blood from the subject and reverses the direction of the blood ... to draw the RBCs (and other components)” from the blood component separation device back to the donor. EX1001, 11:51-56.

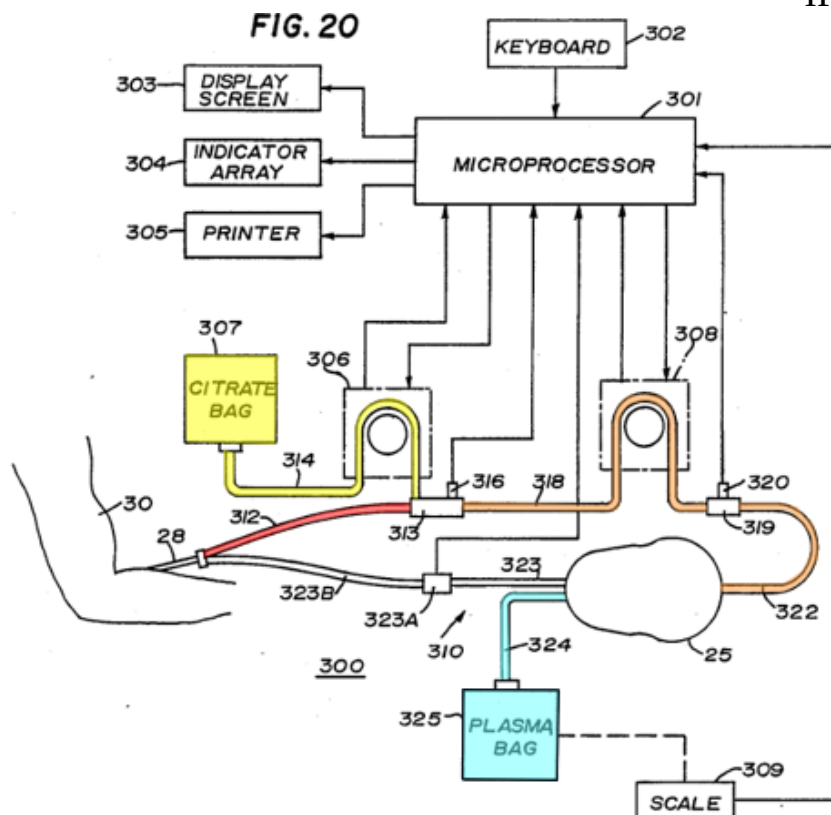
46. As I will explain below, these concepts were well known as of the priority date of the '416 patent.

IX. Prior Art Overview

A. Overview of Lavender

47. Lavender discloses “a system, method and device for continuously fractionating blood in situ.” EX1004, Abstract. Lavender recognized the need to track the volume of anticoagulant collected during a plasma collection procedure to, among other things, “accurately, safely and economically collect[] plasma from a source of blood.” EX1004, 3:26-28.

48. Figure 20 illustrates Lavender’s automatic system 300 for fractionating blood. EX1004, 16:34-53.



EX1004, Fig. 20 (annotated).

49. In Lavender's system 300, a needle or catheter 28 is used to draw whole blood from a donor, which is then mixed with citrate pumped from citrate bag 307. EX1004, 16:57-17:2. Citrate is a blood anticoagulant. EX1004, 16:45-47. The system then pumps the whole blood and anticoagulant mixture to blood fractionator 25, which separates the anticoagulated whole blood into plasma and other blood fractions. EX1004, 5:42-52. The plasma and anticoagulant mixture exits the blood separation device through the plasma line and is collected in plasma bag 325. EX1004, 17:14-16.

50. Lavender's system performs several real-time calculations during the collection process. These calculations account for donor parameters, like hematocrit, as well as a fixed anticoagulant to plasma ratio, which, in turn, relates to a fixed anticoagulant to anticoagulated whole blood ratio. See EX1004, 22:35-39, cols. 41, 42. These calculations also account for the weight of the collected plasma and anticoagulant mixture during the collection process. Ultimately, these calculations are used to calculate the volume of pure plasma and anticoagulant in the plasma collection bag in real time. EX1004, 20:55-68.

51. Below are several of the variables used and/or calculated in Lavender's system:

Variable	Description
CF (conversion factor)	Predetermined ratio (or percentage) of anticoagulant to incoming plasma
QB	Blood flow from donor
TQB	Total blood flow
$HCTD$	Donor's hematocrit
QP	Plasma flow
TQP	Total plasma flow
QCP	Citrate pump rate

<i>TQC</i>	Total citrate (anticoagulant) flow
<i>TDPF</i>	Total dilute plasma (total fluid) in the collection container
<i>TPF</i>	Total plasma filtered (pure plasma) volume in the collection container
<i>TCF</i>	Total citrate (anticoagulant) volume in the collection container

52. During the collection process, these variables are used to monitor the amount of plasma collected. For example, plasma flow (*QP*) is calculated based on the donor's blood flow (*QB*) and hematocrit (*HCTD*). EX1004, 41:4-44:42. *QP* is then used to calculate the citrate pump rate (*QCP*) by multiplying it by the conversion factor (*CF*). *QCP* is used to calculate the total citrate flow (*TQC*). See EX1004, 41:4-44:42. The total plasma volume in the collection container is calculated in real time based on the total volume of fluid in the collection container, determined by the weight of the container, and the plasma dilution factor (*PDF*). See EX1004, 41:4-44:42. The total citrate volume in the collection container (*TPF*) is then calculated in real time based on the total plasma volume in the collection container (*TPF*) and the conversion factor (*CF*). See EX1004, 41:4-44:42.

53. In Lavender, the microprocessor repeatedly performs weight measurements and run-time calculations set forth in Lavender's algorithm and

displays updated values approximately every two seconds. EX1004, 20:55-68.

Lavender's system determines the relationship (ratio) between the pure plasma volume and the anticoagulant volume in the collection container. *See* EX1004, 41:4-44:42. This is then used to determine the pure plasma volume. *See* EX1004, 41:4-44:42. Accordingly, Lavender discloses a determination of pure plasma volume based on the volume of anticoagulant. If any additional conversion or calculation is required, it is my opinion that a POSITA would readily understand how to convert between the two volumes using the same relationship.

54. Lavender executes a main loop of the algorithm until the total plasma filtered (TPF) in plasma bag 325 is equal to or greater than a determined maximum total plasma volume to collect (MAXPF), as determined using a donor's weight. EX1004, cols. 43-44, claim 33.

55. In Lavender, the total plasma volume to collect is 18% of the calculated donor circulating plasma volume. EX1004, 20:10-14, 22:35-46, 41:1-44:42 (Table VI). And the donor circulating plasma volume is calculated based on 5% of donor weight. EX1004, 20:10-14, 22:35-46, 41:1-44:42 (Table VI).

B. Overview of Neyrinck

56. Neyrinck emphasizes the importance of accurately determining total blood volume (TBV) in apheresis procedures to ensure safety and efficacy. EX1005, pp.38-39. Because TBV varies significantly among individuals based on several

physiological variables, Neyrinck outlines multiple methods for calculating TBV—incorporating height, weight, sex, age, and BMI. EX1005, pp.38-39. For example, Neyrinck identifies Nadler’s formula, widely used in apheresis machines, which calculates TBV based on gender, height, weight, and age. EX1005, p.39. Another method uses body mass index (BMI), calculated from weight and height, and assigns a blood volume per kilogram of body weight depending on the BMI category. EX1005, p.40.

57. Neyrinck explains that calculating TBV, extracorporeal volume, and total plasma volume of a donor (TPV) is needed to produce an optimal product while minimizing donor risk. EX1005, p.38. Determining TPV requires both TBV and hematocrit (Hct) values as hematocrit influences a donor’s TPV. EX1005, p.40. For example, where a donor has “a TBV of 5,000 ml and has an Hct of 50% there will be 2,500 mL of plasma, and in case of an Hct of 30% 3,500mL.” EX1005, pp.39-40. This 1,000 mL difference could influence the duration of a plasma exchange procedure. EX1005, pp.39-40.

C. Overview of Bainbridge

58. Bainbridge relates to “a blood component separation device (*e.g.*, a centrifuge)” that separates whole blood into “various blood components” including “plasma and red blood cells.” EX1006, Abstract, ¶0003. Bainbridge’s apheresis

system is designed to improve “collection efficiency” by maximizing “the amount of a particular blood component type” that is collected. EX1006, ¶0006.

59. Bainbridge improves collection efficiency by “continuously and instantaneously monitor[ing] the quantity of RBCs collected ... to determine the instantaneous hematocrit ... of the donor/patient.” EX1006, ¶0302. Bainbridge uses the change in hematocrit to provide “feed[back] adjustment control over certain flow rates” and achieve “the target amount of separated plasma.” EX1006, ¶0302-303. Bainbridge describes that “several advantages can be realized utilizing these procedures for... plasma collections. Such advantages include: ...reduced time requirements for... plasma collections.” EX1006, ¶0304.

60. Bainbridge’s system also administers replacement fluid, such as saline solution, “within the limited range of 80% to 120%” of the donor’s fluid balance percentage to help maintain donor hydration and prevent hypovolemia. EX1006, ¶¶0278, 0282, 0286.

D. Overview of Darashkevich

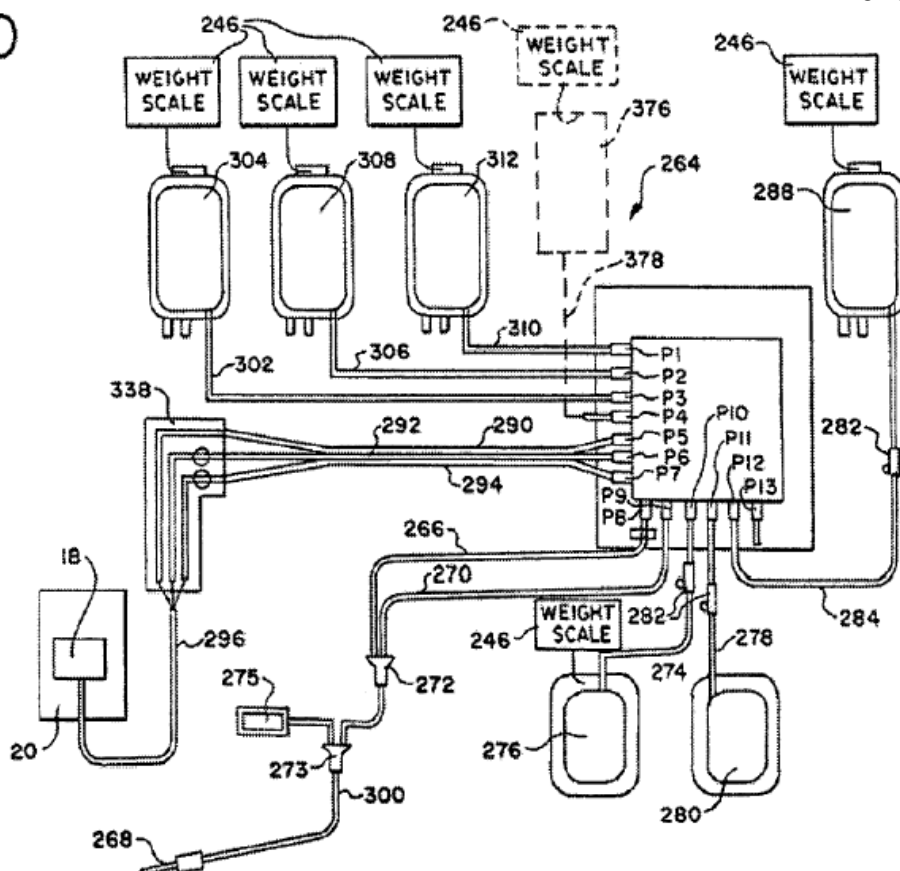
61. Darashkevich discloses methods for removing pathogenic autoantibodies from a patient’s circulation using apheresis. EX1007, ¶0083. In certain embodiments, plasmapheresis removes between approximately 15% to 30% of the patient’s total circulating plasma, effectively reducing the concentration of

harmful autoantibodies. EX1007, ¶0083. Darashkevich's procedure uses discontinuous flow centrifugation using a single venous catheter. EX1007, ¶0083.

E. Overview of Min

62. Min discloses blood processing systems for separating plasma from whole blood. EX1008, 7:4-8:5. Min teaches plasma collection procedures that include a collection cycle, and pre- and post-collection cycles, which include priming the system's tubing by "convey[ing] a predetermined volume of anticoagulant . . . into the in-process container" during the pre-collection cycle. EX1008, 22:41-43; 32:16-18. Figure 10 of Min shows Min's system for performing blood processing procedures, like plasma collection.

FIG. 10



63. In Min, weigh sensors 246 track weight changes and derive fluid processing volumes, including the volume change in anticoagulant container 276 and plasma collection container 304. EX1008, 11:52-55, 17:17-22.

F. Overview of Turgut

64. Turgut discloses separation systems that effectively separate biological material, like blood components, with the help of centrifugal force. EX1009, Abstract. Turgut describes blood separation systems that utilize a centrifuge to separate blood into components and describes using a volume detector to determine

a total volume of fluid within a blood separation system, such as a separation chamber of a centrifuge used to separate blood into components. EX1009, ¶73.

G. Overview of Headley

65. Headley discloses systems and methods for collecting, from whole blood, platelets suspended in plasma, among other blood components. EX1010, Abstract. Headley's blood separation systems use a centrifuge to separate blood into components and use of an array of optical sensors with a control unit to determine a volume of red blood cells within a blood separation system. EX1010, 4:48-64.

H. Overview of Barrett

66. Barrett discloses a hemodialysis patient data acquisition and management system for monitoring blood separation procedures, like hemodialysis. EX1011, 4:14-67. Barrett describes several techniques to monitor hematocrit, including ones used for real-time monitoring during hemodialysis. EX1011, 2:23-57. Barrett specifically discloses determining a patient's hematocrit by dividing a blood sample's calculated total red blood cell volume by a total volume of the blood sample. EX1011, 2:45-49.

X. Identification of How the '416 Patent's Claims are Unpatentable

A. Ground I: Claims 1, 7, 9, 11, 14, and 15 are rendered obvious over Lavender in view of Neyrinck

1. Reasons to Combine Lavender and Neyrinck

67. A POSITA would have found it obvious and would have been motivated to combine Lavender's system with Neyrinck's teachings and would have had a reasonable expectation of success because both relate to the same well-known technologies, both apply substantially similar techniques to achieve similar results, and Lavender's intended functionality would remain substantially the same in the proposed combination.

68. First, a POSITA would have been motivated to combine Lavender and Neyrinck to improve the accuracy and donor-specific customization of Lavender's plasma collection volumes. Lavender calculates plasma collection volumes based on donor-specific data. For example, it calculates a donor's circulating plasma volume, which is 5% of the donor's weight, and then collects 18% of this volume. EX1004, 22:35-46.

69. Similarly, Neyrinck teaches calculating a donor's total plasma volume (TPV) based on donor-specific data when collecting a fixed volume of plasma. EX1005, pp.39-40. Neyrinck teaches how to calculate TPV using the donor's total blood volume (TBV)—calculated based on donor weight, height and hematocrit—and explains that hematocrit can affect the plasma volume being collected. EX1005, pp.39-40. *See also* §IX.B. A POSITA would readily recognize that incorporating Neyrinck's TPV calculation—based on TBV and hematocrit—into Lavender's system, would allow Lavender's system to calculate a more accurate and

individualized target plasma collection volume because it would consider individualized information like height and hematocrit. See §IX.B.

70. Second, Lavender and Neyrinck both relate to plasma apheresis and using donor-specific information to determine donor plasma volume. Lavender collects plasma based on a donor's circulating plasma volume; calculated using the donor's weight. EX1004, 1:12-13, 22:35-46. Similarly, Neyrinck teaches collecting plasma based on a donor's weight, height, and hematocrit. EX1005, p.39. Therefore, a POSITA would have had a reasonable expectation of success combining Lavender with Neyrinck because both relate to the same well-known technologies of using donor information to calculate donor plasma volume.

71. Third, Lavender and Neyrinck apply substantially similar techniques to achieve similar results. Lavender calculates the donor's circulating plasma volume as 5% of bodyweight and collects 18% of that volume. EX1004, 1:12-13, 22:35-46. Neyrinck similarly utilizes donor data like weight and height to calculate TBV and uses the calculated TBV and hematocrit to calculate TPV. EX1005, p.39-40. Both systems similarly use donor-specific information to determine a safe and effective plasma collection volume. EX1004, 3:26-28; EX1005, p.38. Thus, both references consider donor-specific input to determine how much plasma can be safely and efficiently collected. Because both systems are focused on achieving similar results—determining the total plasma collection volume—and consider similar

variables in determining that amount, a POSITA would have had a reasonable expectation of success in implementing Neyrinck's TPV calculation in Lavender's system.

72. Further, Lavender's functionality would remain substantially the same in the proposed combination. As discussed above, Lavender calculates collection volumes based on donor-specific information like weight and hematocrit. EX1004, 20:10-21; 22:35-46. Neyrinck's formulas determine TBV and TPV using similar donor inputs (*e.g.*, weight, height, and hematocrit). EX1005, p.39-40. Thus, Neyrinck's plasma collection calculations could be readily implemented in Lavender's computational framework. In one such example, Lavender's system could implement Neyrinck's TPV calculation, which considers donor hematocrit, to more accurately calculate a target plasma collection volume and improve collection yield. Additionally, Lavender recognizes that "various modifications and alterations may be made therein without departing from the true scope and spirit of the present invention." EX1004, 45:1-7. Therefore, a POSITA would have had a reasonable expectation of success in combining Lavender with Neyrinck.

2. Claim 1

- a. 1[preamble] A method for collecting plasma comprising:**

73. To the extent the preamble is limiting, Lavender discloses a system, method and device for fractionating blood “to **collect blood substances, such as plasma.**” EX1004, Abstract, 1:12-13, claim 1 (“A method of collecting plasma....”), 5:42-49, 1:48-56.

b. 1[a] determining a weight and height of a donor;

74. Lavender determines a donor’s weight through “entry and validation of donor data, including ... **donor weight in pounds.**” EX1004, 20:10-14, Abstract.

75. Neyrinck calculates a donor’s TBV using the donor’s **weight** and **height**, according to Nadler’s formula. EX1005, pp.38-40.

76. As discussed in §X.A.1, it is my opinion that a POSITA would have been motivated to incorporate, and would have had a reasonable expectation of success incorporating, Neyrinck’s use of donor’s weight and height in Lavender’s system to calculate TBV and then more accurately calculate donor plasma volume.

c. 1[b] determining a hematocrit of the donor;

77. Lavender determines a hematocrit of the donor through “entry and validation of donor data, including ... **donor hematocrit in percent.**” EX1004, 20:10-14.

78. Neyrinck discloses calculating a donor’s TPV using a donor’s hematocrit and TBV. EX1005, pg. 39-40, Fig. 3.

d. 1[c] calculating a donor plasma volume based, at least in part, on the weight and height of the donor and the hematocrit of the donor;

79. Lavender in view of Neyrinck renders obvious limitation 1[c].

80. Lavender calculates a **donor's circulating plasma volume** as 5% of donor **weight**. Lavender then collects 18% of that calculated volume. EX1004, 22:39-46; EX1005, 20:10-14, 22:35-46, 41:1-44:42 (Table VI).

81. Neyrinck discloses calculating TBV based on donor **height** and **weight** using either Nadler's formula or BMI. EX1005, p.39. After calculating the TBV, Neyrinck calculates a donor's total plasma volume (**TPV**) based on the donor's TBV and **hematocrit** (Hct) using the equation:

$$TPV = TBV * (1 - Hct)$$

EX1005, p.39-40, Fig. 3. Thus, Neyrinck's TPV calculation is based on the donor's weight and height (used to calculate TBV) and hematocrit.

82. As discussed in §X.A.1, it is my opinion that a POSITA would have been motivated to incorporate Neyrinck's TPV calculation into Lavender's system to more accurately calculate a donor's plasma volume. Neyrinck's method uses donor inputs already considered by Lavender (weight and hematocrit) and also uses the donor's height to yield a more individualized TBV. EX1005, p.38-40. Thus, a POSITA would recognize that replacing Lavender's simplified 5% body weight estimate for TPV with Neyrinck's TPV calculation based on both height and

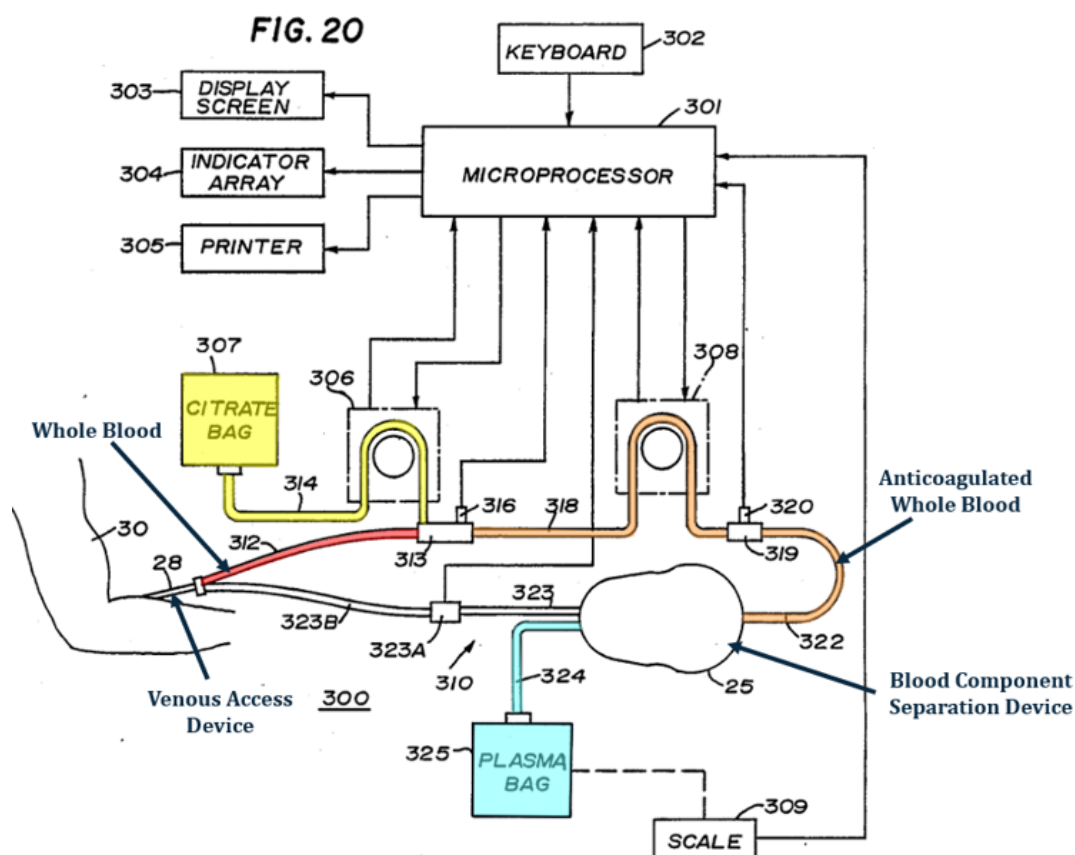
hematocrit would improve donor safety and product yield. Also, a POSITA would have had a reasonable expectation of success when incorporating Neyrinck's donor plasma volume into Lavender's system. *See* §X.A.1.

e. 1[d] calculating a target plasma collection volume based, at least in part, on the calculated donor plasma volume and a target percentage of plasma;

83. Lavender calculates a target plasma collection volume that is 18% of a donor's circulating plasma volume. EX1004, 22:39-46. It is my opinion that this target plasma collection volume is thus based, at least in part, on Neyrinck's TPV calculation and the 18% target percentage of plasma.

f. 1[e] withdrawing whole blood from the donor through the venous-access device and a first line, the first line connected to a blood component separation device;

84. Lavender withdraws whole blood through the venous-access device. A pump "pump[s] blood from the donor" through needle 28, tubes 312, 318, 322, and into fractionator 25, shown below in Figure 20. EX1004, 5:18-22, Fig. 20.



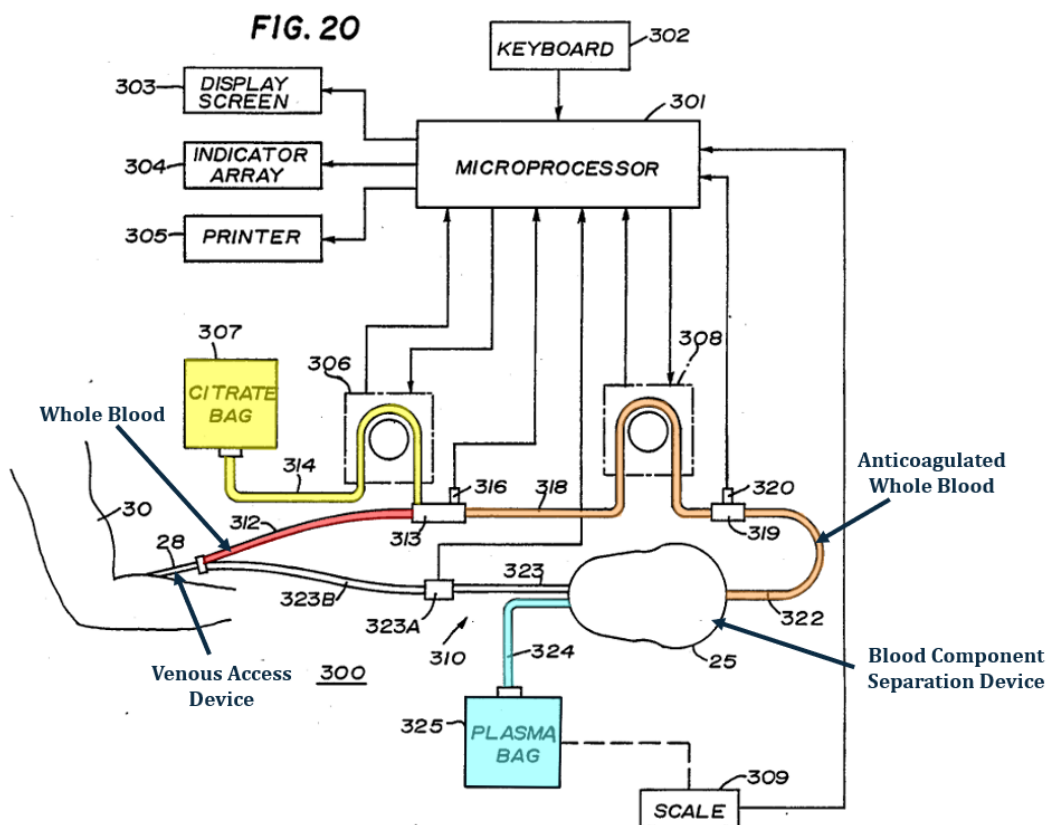
EX1004, Fig. 20 (annotated). The drawn blood is whole blood because it is a mixture of “a variety of blood fractions.” EX1004, 5:45.

85. The draw line is connected to blood fractionator 25, as “[t]he blood fractionator has an inlet ..., the inlet being connected to the donor by a blood tube.” EX1004, 5:13-16, Figs. 1, 20.

86. Blood fractionator 25 is a blood component separation device because “it produces a variety of blood fractions,” including plasma, from whole blood. EX1004, 5:42-45.

- g. 1[f] introducing anticoagulant into the withdrawn whole blood through an anticoagulant line;**

87. In Lavender, “[a] supply of anticoagulant 35 is connected to the tube 27” supplying withdrawn whole blood from the donor. EX1004, 5:22-28, Figs. 1, 20. “[A] second pump 31A ...provide[s] a predetermined flow rate ... of anticoagulant with the blood flowing from the donor 30 to the fractionator” via anticoagulant line 314. EX1004, 5:22-28, Figs. 1, 20 (tube 314).



EX1004, Fig. 20 (annotated).

- h. 1[g] separating the withdrawn whole blood into a plasma component and at least a second blood component using the blood component separation device;**

88. In Lavender, the withdrawn whole blood flows into Lavender's blood fractionator 25, which separates it into blood fractions (components), including a plasma component and a component containing red blood cells, white blood cells, and platelets (*i.e.*, at least a second blood component). EX1004, 1:21-25, 5:42-52, 10:58-11:6, Figs. 1, 20.

i. 1[h] collecting the plasma component from the blood component separation device and into a plasma collection container;

89. Lavender discloses that after the blood fractionator separates the components, "a plasma outlet port ... allows **plasma** to flow to a plasma collection bag" via tubing (*e.g.*, tubing 324 in Fig. 20). EX1004, 10:58-11:6, Figs. 1, 4, 15, 17, 20.

j. 1[i] calculating a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma collection container;

90. Lavender calculates a volume of anticoagulant collected in the collected plasma component as the plasma component is being collected in the plasma collection container. Lavender weighs the collected plasma and anticoagulant solution in plasma bag 325 (*TDPW* (total dilute plasma filtered in grams)), transmits the weight to microprocessor 301, and uses this weight to calculate the volume of plasma and anticoagulant in plasma bag 325 (*TDPF*). EX1004, 16:34-53, 41:1-44:33 (Table VI, §5). *TDPF* is then multiplied by plasma factor *PDF*, determined using

the predefined ratio of citrate added per milliliter of plasma to dilute incoming plasma to 68% of the initial concentration, to calculate the total amount of **filtered plasma (TPF)**. Then, *TPF* is multiplied by conversion factor (*CF*)³, which is determined using a predefined ratio of citrate added per milliliter of plasma, to calculate the volume of anticoagulant in plasma bag 325 (*i.e.*, **total citrate filtered (TCF)**). EX1004, 16:50-53, 22:35-46, 17:14-16, 41:1-44:33 (Table VI, §5(B)). These calculations are part of Lavender’s main loop. EX1004, 41:1-44:33 (Table VI, §5(B)).

91. Lavender’s microprocessor repeatedly measures *TDPW* in real-time and updates the above-identified calculated values. EX1004, 20:55-68, 41:1-44:33. Specifically, Lavender discloses “repeatedly performing the measurements and calculations . . . updating these values each time the program cycles through the main loop, and displaying the values in ‘Run’-message (Table V) which is updated approximately every two seconds.” EX1004, 20:55-68, 41:1-44:33.

³ Note that Table VI has two “CF” terms, (i) conversion factor (*CF*) and (ii) the rate citrate is pumped into the donor’s whole blood (citrate filtered in ml/min (*CF*)). This appears to be a typographical error and a POSITA would readily understand that the “CF” in the total citrate filtered (*TCF*) equation is conversion factor (*CF*).

92. Lavender thus calculates the anticoagulant volume as the plasma component is being collected in the plasma collection container by repeatedly performing the *TCF* calculation until the total plasma filtered is equal to or greater than the maximum total plasma filtered. EX1004, cols. 43-44.

k. **1[j] calculating a volume of pure plasma collected within the plasma collection container based, at least in part, on the calculated volume of anticoagulant in the collected plasma component; and**

93. Lavender uses the amount of anticoagulant (citrate) added to the whole blood to calculate the total pure plasma volume collected. EX1004, 20:55-68, 41:1-44:33. As discussed with respect to claim limitation 1[i], *supra* §X.A.2.j, it is my opinion that Lavender calculates **total plasma filtered (*TPF*)** by multiplying the total amount of dilute plasma filtered (*TDPF*) by plasma dilution factor (*PDF*) (*i.e.*, ***TPF* = *TDPF* * *PDF***). EX1004, 20:55-68, 22:35-46, 41:1-44:33. As discussed above, *PDF* is determined using the predefined ratio of citrate added per milliliter of plasma to dilute incoming plasma to 68% of the initial concentration. EX1004, 22:35-46.

94. Next, Lavender calculates the anticoagulant volume in the plasma container (*i.e.*, **total citrate filtered (*TCF*)**). See §X.A.2.i.

95. As shown in the annotated excerpt of §5(B) of Table VI below, the volume of pure plasma in the plasma collection bag (***TPF***) and the volume of

anticoagulant in the plasma container (**TCF**) share a direct mathematical relationship. EX1004, 41:1-44:33 (Table VI, §5(B)).

$$\begin{array}{ll}\text{TPF}=\text{TDPF}*\text{PDF} & \text{(total plasma filtered, ml)} \\ \text{CF}=\text{PF}*\text{CF} & \text{(citrate filtered, ml/min)} \\ \text{TCF}=\text{TPF}*\text{CF} & \text{(total citrate filtered, ml/min)}\end{array}$$

96. That is, during collection, any change in the calculated value of the volume of anticoagulant (**TCF**) requires a corresponding change in the calculated value of the volume of pure plasma (**TPF**), and vice versa. Both **TCF** and **TPF** are based on the predefined ratio of citrate added per milliliter of plasma to dilute incoming plasma to 68% of the initial concentration. EX1004, 22:35-46. Accordingly, the volume of pure plasma collected in the plasma collection bag (**TPF**) is calculated in real-time based “at least in part” on the calculated volume of anticoagulant in the collected plasma component (**TCF**) because both **TPF** and **TCF** are dependent on the predefined ratio of citrate added per milliliter of plasma to dilute incoming plasma to 68% of the initial concentration and as one value changes, the other necessarily changes.

97. It is my opinion that Lavender’s disclosure of the dependency of both **TPF** and **TCF** on the predefined ratio of citrate added per milliliter of plasma discloses calculating a volume of pure plasma collected in the plasma collection bag

(*TPF*) based, at least in part, on a calculated volume of anticoagulant in the collected plasma component (*TCF*).

98. The plain and ordinary meaning of the term “based, at least in part, upon” suggests that the calculation may rely on one or more methods and the ’416 patent does not disavow interpreting “based, at least in part, on” to encompass a direct relationship between the pure plasma volume in the collection container and the volume of anticoagulant in the collected plasma component.

99. Alternatively, it is my opinion that a POSITA would have found this limitation obvious in view of Lavender’s disclosures because of the interdependency between the predefined ratio of citrate added per milliliter of whole blood, *TPF* and *TCF*, and the understanding that the plasma volume in the collection bag is based, at least in part, on the volume of anticoagulant in the collection bag.

I. 1[k] continuing steps (e) through (i) until the calculated volume of pure plasma collected within the plasma collection container equals the target plasma collection volume.

100. As discussed above, Lavender performs steps (e)–(i). See §§X.A.2.f-k.

101. When a blood separation procedure starts, Lavender’s system initializes the system algorithm of Table VI. EX1004, 20:55-68, 41:1-44:33, Figs. 25A-25D. The Main Loop of the algorithm is repeated by “introducing anticoagulant to the blood from which the plasma is to be collected ... separating plasma from the

extracted blood ... **until a predetermined ... volume of plasma has been collected.**”⁴ EX1004, 21:62-22:6, 46:14-22, claim 1.

3. **Claim 7: A method according to claim 1, further comprising: calculating the donor's body mass index based, at least in part on the weight and height of the donor, the donor plasma volume calculated based, at least in part, on the donor's body mass index.**

102. Lavender in view of Neyrinck renders obvious claim 7.

103. Neyrinck teaches calculating TBV based on a donor's **body mass index** (BMI), which is calculated using both **height** and **weight**. EX1005, pp.39–40. Specifically, Neyrinck explains that “based on the BMI the bodyweight of the person needs to be multiplied with a number as given in Table III to achieve the TBV.” EX1005, pp.39–40.

104. After calculating the TBV, Neyrinck calculates the **donor's total plasma volume** (TPV) using TBV and a donor's **hematocrit** (Hct) via equation:

$$TPV = TBV * (1 - Hct)$$

EX1005, p.39-40.

105. As discussed in §X.A.1, it is my opinion that a POSITA would have been motivated to incorporate Neyrinck's TPV equation (*e.g.*, using the **TBV based on BMI**) into Lavender's system to improve collection accuracy and donor safety.

⁴ All emphasis added unless otherwise noted.

4. **Claim 9: A method according to claim 1, further comprising: inserting a venous-access device into the donor prior to step (e).**

106. Lavender's needle is inserted in the donor's vein before the user presses the START button to initialize the system algorithm to turn on the blood pump to withdraw blood. EX1004, 5:13-22, 20:48-54, Figs. 1, 20.

5. **Claim 11: A method according claim 1, further comprising: determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the number of rotations of the anticoagulant pump.**

107. Lavender determines a volume of anticoagulant introduced into the whole blood based on a number of rotations of the anticoagulant pump. EX1004, 41:27-30, 42:8-44:32. Lavender's system 300 uses anticoagulant pump 306 "for pumping anticoagulant from an associated source" into "the blood flowing from the donor 30 to the fractionator 25." EX1004, 15:47-53, 16:45-47, 16:54-17:2, claim 1, Fig. 20. Lavender introduces anticoagulant into the whole blood at "a predetermined flow rate," which Lavender expresses in its algorithm as QC . EX1004, 5:25-26. Lavender sets the citrate pump flow rate, QCP , to QC . EX1004, cols. 41, 42. Further, in the Main Loop, Lavender determines TQC , total citrate flow, based on QCP , the citrate pump rate, which depends on the number of rotations of the citrate pump ($CRPM$).

108. It is my opinion that Lavender also calculates the volume of anticoagulant in the collected plasma component based on the number of rotations of the anticoagulant pump. Lavender discloses that “[t]he flow rate of the anti-coagulant and the blood are **fixed by the pumps** 31 and 31A used in conjunction with the supply 35 of anti-coagulant.” EX1004, 15:47-53. Further, as shown in §2 of Table VI, the rotations of citrate pump (**CRPM**) and blood pump (**BRPM**) are calculated based on the citrate pump flow rate (**QCP**) and blood pump flow rate (**QBP**). See Table VI, §2. As shown in the calculation below, the citrate and blood flow rates (**QCP** and **QBP**) both depend on **CF**. Thus, citrate and blood pump rotations (**CRPM** and **BRPM**) depend on **CF**.

$$QCP = QC = QP * CF = QB * (1 - HCTD) * CF, \text{ and}$$

$$QBP = QB + QC = QB + QCP$$

$$= QB + QP * CF$$

$$= QB + QB * (1 - HCTD) * CF$$

109. Accordingly, as the calculations in the main loop (*e.g.*, volume of plasma filtered (**TPF**) and volume of citrate filtered (**TCF**)) depend on **CF** and **PDF**, whose values, along with predetermined blood flow rate **QB** and hematocrit **HCTD**, determine the citrate and blood pump rotations (**CRPM** and **BRPM**), the calculated volume of anticoagulant in the collected plasma component (**TCF**) is determined and

calculated based, at least in part, on the number of rotations of the anticoagulant pump (citrate pump **CRPM**). For example, as discussed above, $QC = QP * CF$ and $QP = QB * (1 - HCTD)$, so

$$CF = \frac{QC}{QP} = \frac{QC}{[QB*(1-HCTD)]}$$

Since $QBP = QB + QC = QB + QCP$,

$$CF = \frac{QCP}{[(QBP-QCP)*(1-HCTD)]}$$

Hence, once CF is set and $HCTD$ is known, it is my opinion that Lavender determines the pump rates. Since CF determines the pump rates and is used to calculate the volume of anticoagulant in the collected plasma component, the calculated volume of anticoagulant in the collected plasma component is based, at least in part, on the number of rotations of the anticoagulant pump.

6. **Claim 14: A method according to claim 1, further comprising: monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection container based, at least in part, on the monitored volume of collected plasma component.**

110. Lavender monitors a volume of plasma component (*e.g.*, $TDPF$ total dilute plasma filtered) collected within the plasma collection container. EX1004, 43:4-6. As discussed above in §X.A.2.i., Lavender updates $TDPF$ as the system withdraws blood.

111. Lavender uses the monitored volume of collected plasma component (*e.g.*, *TDPF*) to calculate a volume of pure plasma (*e.g.*, *TPF* total plasma filtered) in the plasma component (*e.g.*, *TPF* is the product of *TDPF* and *PDF*, the plasma dilution factor). EX1004, 41:1-44:40. Therefore, the volume of pure plasma collected within the plasma collection container is based, at least in part, on the monitored volume of the collected plasma component.

7. Claim 15: A method according to claim 1, further comprising: monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection container based, at least in part, on the monitored weight of collected plasma component

112. Lavender monitors a weight of plasma component (*e.g.*, *TDPW* total weight of dilute plasma filtered) collected within the plasma collection container. See EX1004, 41:1-44:40 (Table VI, §5(B)). Lavender discloses that the current total volume of pure plasma in the collection container (*TPF*) is based on the *TDPF* (“the monitored volume of collected plasma component”) which is based on the weight of the collected plasma component (*TDPW*). EX1004, 41:1-44:33.

B. Ground II: Claims 2-6, 17-22, 24, 26, 28, and 29 are rendered obvious over Lavender in view of Neyrinck and further in view of Bainbridge.

1. Reasons to Combine Lavender, Neyrinck, and Bainbridge.

113. As discussed above in §X.A.1 (Ground I), it is my opinion that a POSITA would have been motivated to modify Lavender’s system in view of

Neyrinck. Additionally, a POSITA would have been motivated to modify the Lavender and Neyrinck system with Bainbridge and would have had a reasonable expectation of success in doing so because all relate to plasma apheresis, all apply substantially similar techniques to achieve similar results, and the functionality of the Lavender and Neyrinck system would not change with the addition of Bainbridge.

114. A POSITA would have been motivated to combine Lavender, Neyrinck, and Bainbridge to improve plasma collection efficiency and to ensure donor safety by avoiding dehydration. Lavender discloses a membrane-based blood fractionator. EX1004, 6:3-12. Bainbridge discloses a blood apheresis system including a single needle and a single interconnect tubing 38 to draw and return the donor's blood. EX1006, ¶0091, Fig. 2a. Interconnect tubing 38 is connected to a centrifuge to separate blood into various blood components (*e.g.*, plasma, red blood cells). EX1006, ¶¶0086-87, Fig. 2a.

115. Lavender's system draws a donor's blood and pumps the blood into membrane-based blood fractionator 25 to separate the blood into blood components including plasma and red blood cells. EX1004, 1:21-25, 5:11-23. Bainbridge's system draws a donor's blood and pumps it into a centrifuge-type blood processing vessel to separate the blood into blood component types (*e.g.*, plasma, red blood cells). EX1006, ¶¶0086-87. It was generally known in the art that a centrifuge-based

blood separation device, provided comparable treatment in less time than a membrane-based blood separation device. *See* EX1012, p.135. Therefore, a POSITA would have been motivated to modify the Lavender and Neyrinck system in view of Bainbridge's centrifuge-based collection device to more efficiently separate plasma from a donor's blood and reduce the overall procedure time.

116. Additionally, a POSITA would have been motivated to incorporate Bainbridge's centrifuge-based blood separation system with a single draw and return tubing into Lavender's system to administer appropriate amounts of replacement fluid during the plasma collection return cycle. EX1006, ¶¶0015, 0090, Figs. 2A-2D. Bainbridge's system administers replacement fluid, such as saline solution, based on a donor's fluid balance percentage "within the limited range of 80% to 120%" during a return cycle to maintain donor hydration and prevent hypovolemia or related reactions. EX1006, ¶¶0278, 0282-286. Therefore, a POSITA would have been motivated to modify Lavender and Neyrinck in view of Bainbridge because incorporating Bainbridge's fluid balance feature in Lavender would ensure donor safety by avoiding dehydration and hypovolemia.

117. Additionally, a POSITA would have had a reasonable expectation of success in making the proposed combination because Lavender, Neyrinck, and Bainbridge all relate to plasma apheresis. Lavender collects plasma based on donor information. EX1004, 1:12-13, 22:35-46. Neyrinck also teaches using donor-

specific information in plasma collection. EX1005, p.39. Similarly, Bainbridge relates to “a blood component separation device (*e.g.*, a centrifuge)” that separates whole blood into “various blood components” including “plasma.” EX1006, ¶0003. Bainbridge also determines target collection volumes using donor data, like weight and height. EX1006, Figs. 33-35, ¶¶0071-73, 0303, 0336-340.

118. Further, implementing Bainbridge’s centrifuge blood processing system would not alter the core functionality of Lavender’s system, as Lavender already separates plasma from whole blood like Bainbridge’s system. Additionally, Lavender recognizes that “various modifications and alterations may be made therein without departing from the true scope and spirit of the present invention.” EX1004, 45:1-7. Therefore, it is my opinion that a POSITA would have been motivated to incorporate Bainbridge’s centrifuge-type blood processing vessel system with a single draw and return tubing for administering replacement fluid to improve plasma separation efficiency and keep the donor hydrated and prevent hypovolemia, and would have had a reasonable expectation of success in doing so as the systems use substantially similar techniques to achieve similar results so the proposed modification would have achieved predictable results.

2. **Claim 2: A method according to claim 1, further comprising: returning, after collecting at least a portion of the target plasma collection volume, the contents of the blood component separation device to the donor through the first line.**

119. Lavender in view of Neyrinck and Bainbridge renders obvious claim 2.

120. Lavender **returns** contents (*e.g.*, red blood cells) of blood fractionator 25 to the donor through a blood outlet port during plasma collection. EX1004, 1:21-25, 10:58-63, Fig. 20.

121. Bainbridge discloses blood removal/return tubing assembly 20 that is configured to draw blood and **return** the contents of blood processing vessel 352 **through interconnect tubing** 38 after collecting plasma from a donor. EX1006, ¶¶0091, 0306, Fig. 2a.

122. As discussed in §X.B.1, it is my opinion that a POSITA would have been motivated to combine the Lavender-Neyrinck system with Bainbridge's centrifuge-type components to incorporate a single interconnect tubing for drawing and returning blood/components and would have had a reasonable expectation of success in doing so.

3. Claim 3: A method according to claim 2, further comprising: calculating an intravascular deficit based, at least in part on, the volume of pure plasma collected and a volume of the contents of the blood component separation device returned to the donor.

123. As discussed in §X.B.2, (claim 2), it is my opinion that Lavender in view of Neyrinck and Bainbridge discloses returning contents of the blood component separation device to the donor.

124. Bainbridge further discloses administering replacement fluid, such as

saline solution, based on a donor's fluid balance percentage (target intravascular deficit) within the limited range of 80% to 120% (*e.g.*, "80% representing the lessened amount of fluid the donor/patient 4 is given back ... thus, if 80% is chosen for example, then the donor/patient 4 ends the procedure with 80% of the donated fluid volume.") to maintain donor hydration and prevent hypovolemia or related reactions. EX1006, ¶¶0278, 0282, 0285-286. The amount of replacement fluid to return to the donor/patient is based on the **total collection flow rate** minus the flow rate of the anticoagulant inflow multiplied by the total fluid balance percentage. EX1006, ¶¶0278, 0282, 0285-286. Accordingly, Bainbridge's intravascular deficit is based on the total blood collection flow that includes both the volume of pure plasma collected and the volume of the contents of the blood component separation device returned to the donor.

125. As discussed in §X.B.1, it is my opinion that a POSITA would have been motivated to incorporate Bainbridge's centrifuge-type components and use of fluid balance percentage for administering replacement fluid into Lavender's system to improve collection efficiency, maintain donor hydration, and prevent hypovolemia, and would have had a reasonable expectation of success in doing so.

4. Claim 4: A method according to claim 3, further comprising: returning a volume of saline to the donor to obtain a target intravascular deficit.

126. As discussed in §X.B.3, (claim 3), Lavender in view of Neyrinck and

Bainbridge discloses calculating an intravascular deficit.

127. Bainbridge further discloses administering **replacement fluid**, such as **saline solution**, based on a donor's **fluid balance percentage** (target intravascular deficit) within the limited range of 80% to 120% to maintain donor hydration and prevent hypovolemia or related reactions. EX1006, ¶¶0278, 0282, 0285-286.

5. Claim 5: A method according to claim 4, wherein the target intravascular deficit is 0 milliliters.

128. As discussed in §X.B.4, (claim 4), Lavender in view of Neyrinck and Bainbridge discloses obtaining a target intravascular deficit.

129. As discussed above, Bainbridge discloses maintaining a donor's fluid balance within a range of 80% to 120%. EX1006, ¶¶0278, 0282, 0285-286. A POSITA would understand that a fluid balance of 100% (between 80% and 120%) corresponds to an intravascular deficit of 0 milliliters. Choosing 100% (0 milliliters) from the limited range of 80% to 120% for the fluid balance percentage would have been an obvious design choice, as it is the natural and predictable result of operating within Bainbridge's disclosed range. EX1006, ¶¶0278, 0282, 0285-286. Further, Bainbridge's range encompasses the claimed value, establishing a prima facie case of obviousness.

6. Claim 6: A method according to claim 4, wherein the target intravascular deficit is between -250 and 500 milliliters.

130. As discussed in §X.B.4, (claim 4), Lavender in view of Neyrinck and

Bainbridge discloses obtaining a target intravascular deficit.

131. As discussed above, it would have been obvious to a POSITA to choose 0 milliliter as the target intravascular deficit. *See* §X.B.5 (claim 5).

132. As 0 milliliters is between -250 and 500 milliliters, Lavender in view of Neyrinck and Bainbridge renders obvious this claim. *See* §X.B.5 (claim 5).

7. Claim 17

a. 17[preamble] A system for collecting plasma comprising:

133. *See* §X.A.2.a (1[preamble], Ground I).

b. 17[a] a venous-access device for drawing whole blood from a donor and returning blood components to the donor;

134. *See* §X.A.2.f (1[e], Ground I).

c. 17[b] a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container;

135. *See* §§X.A.2.f, X.A.2.h-i (Ground I: 1[e], 1[g], 1[h]).

d. 17[c] a first line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device and return fluid within the blood component separation device to the donor, the flow through the first line being controlled by a first pump;

136. *See* §§X.A.2.f (1[e], Ground I), X.B.2 (claim 2).

137. Lavender in view of Neyrinck and Bainbridge renders obvious returning fluid within the blood component separation device to the donor through the first line. *See* §X.B.2 (claim 2).

- e. **17[d] an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and**

138. *See* §X.A.2.g (1[f], Ground I).

- f. **17[e] a controller configured to control the operation of the blood component separation device and the first pump,**

139. *See* §X.A.2.i, (1[h], Ground I).

140. Lavender discloses a microprocessor that “operates under program control to calculate, based on the donor data, the amount of plasma to be collected and the amount of anticoagulant to be added ... controls the operation of the extracorporeal devices, regulates the operating parameters, and stops the procedure when the predetermined amount of plasma has been obtained.” *See* EX1004, Abstract. The program thus controls the fractionator (blood component separation device) and the associated fluid pumps. EX1004, 18:27-64, claims 28, 29, 33, 35, 36, 38, and 40-41.

- g. **17[f] the controller configured to calculate (1) a donor plasma volume based, at least in part, on a weight and height of the donor and a hematocrit of the donor**

141. *See* §X.A.2.d (1[c], Ground I).

- h. 17[g] (2) a target plasma collection volume based, at least in part, on the calculated donor plasma volume and a target percentage of plasma,**

142. See §X.A.2.e (1[d], Ground I).

- i. 17[h] (3) a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma container, and**

143. See §X.A.2.j (1[i], Ground I).

- j. 17[i] (4) a volume of pure plasma collected within the plasma container based, at least in part, upon the volume of anticoagulant in the collected plasma component,**

144. See §X.A.2.k (1[j], Ground I).

- k. 17[j] the controller configured to stop the first pump when the calculated volume of pure plasma collected within the plasma container equals the target plasma collection volume.**

145. See §X.A.2.l (1[k], Ground I).

- 8. Claim 18: A system according to claim 17, wherein the controller is further configured to: return, after collecting at least a portion of the target plasma collection volume, fluid remaining within the blood component separation device via the first line.**

146. See §§X.B.7.a-k, X.B.2 (claim 17, claim 2).

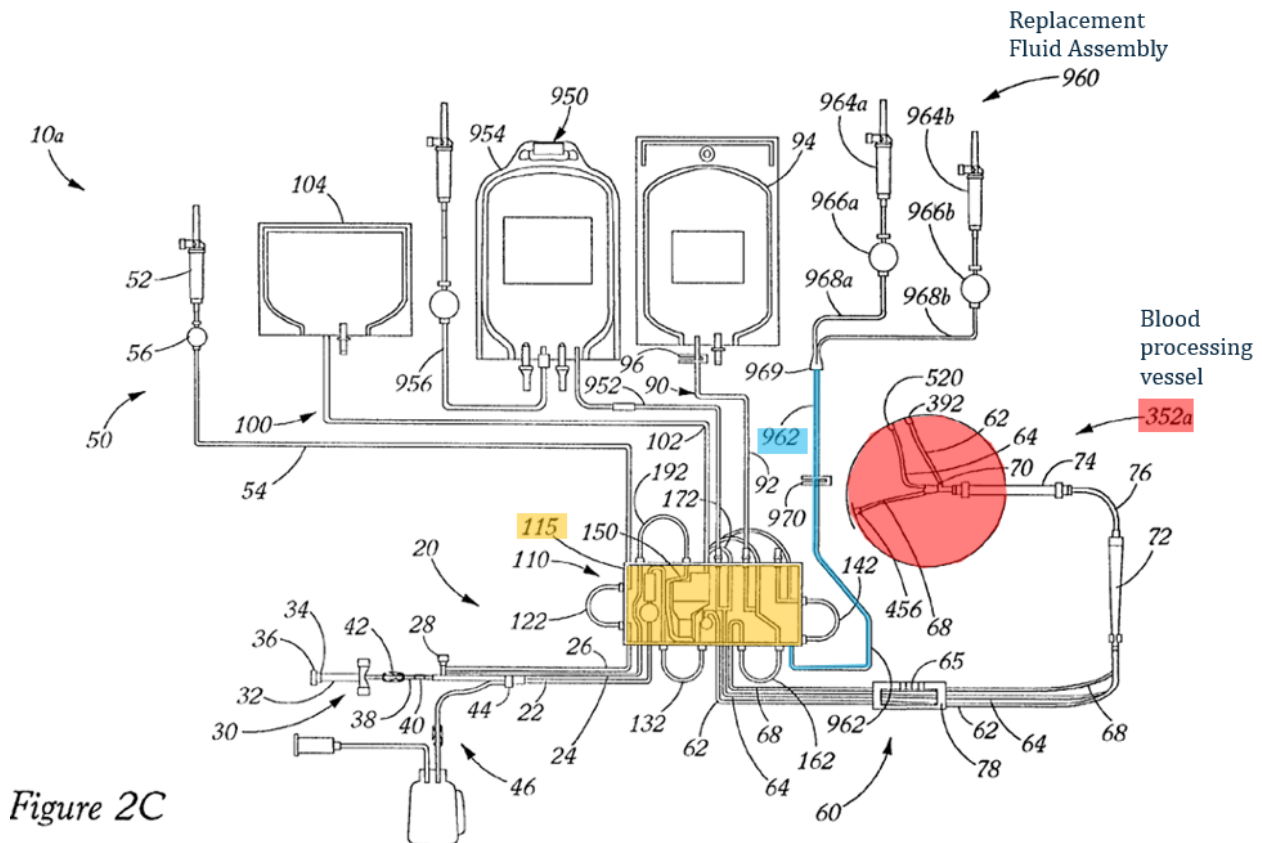
- 9. Claim 19: A system according to claim 18, wherein the controller is further configured to: calculate an intravascular deficit based, at least in part on, the volume of pure plasma collected and a volume of the contents of the blood component separation device returned to the donor.**

147. See §§X.B.8, X.B.3 (claim 18, claim 3).

- 10. Claim 20: A system according to claim 19, further comprising: a saline line configured to fluidly connect to a saline source and the blood component separation device, the controller configured to return a volume of saline to the donor to obtain a target intravascular deficit.**

148. See §§X.B.9, X.B.4 (claim 19, claim 4).

149. Bainbridge further discloses replacement fluid (*e.g.*, saline) tubing line 962 (blue) fluidly connected to a fluid source (not shown) and blood processing vessel 352a (red) via cassette member 115 (yellow). EX1006, ¶¶0278, 0282, 0285-286, Figs. 2C-D.



11. **Claim 21: A system according to claim 20, wherein the target intravascular deficit is between –250 and 500 milliliters.**

150. See §§X.B.10, X.B.6 (claim 20, claim 6).

12. **Claim 22: A system according to claim 17, wherein the controller is further configured to: calculate the donor's body mass index based, at least in part, on the weight and height of the donor, the donor plasma volume calculated based, at least in part, on the donor's body mass index.**

151. See §§X.B.7.a-k (claim 17), X.A.3 (claim 7, Ground I).

13. **Claim 24: A system according to claim 17, wherein the volume of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the donor's hematocrit.**

152. See §§X.B.7.a-k (claim 17).

153. The combination of Lavender, Neyrinck, and Bainbridge further discloses claim 24 under the plain and ordinary meaning of the term “based, at least in part, upon.” The claim language itself—“based, at least in part, upon”—suggests that the calculation may rely on interrelated methods and not just a single, exclusive approach. While the ’416 patent provides an equation for calculating the percentage of anticoagulant in the collected plasma (AC %) based on the donor’s hematocrit, it does not specify how the volume of anticoagulant in the collected plasma is calculated. The specification states that “[o]nce the technician/system 100 has calculated the percentage of anticoagulant within the plasma collection container

216 ... the technician/system 100 may determine the volume of anticoagulant within the container (based on the percentage of anticoagulant within the container 216).” EX1001, 11:29-36. As explained below, Lavender expressly discloses claim 24 under the plain and ordinary meaning of “based, at least in part, upon.”

154. In Lavender’s automatic system 300, the user enters donor data, including **hematocrit**, weight, and sex, before initializing the system algorithm. EX1004, 20:10-14, 55-67. The algorithms shown in Table VI use donor data, including hematocrit (**HCTD**), to calculate various interrelated equations. EX1004, 41:1-44:42 (Table VI). These equations determine collection volumes like the citrate (anticoagulant) volume (**TCF**) and the pure plasma volume (**TPF**). EX1004, 41:1-44:42 (Table VI).

155. It is my opinion that Lavender’s calculation of the volume of total citrate filtered (anticoagulant) in plasma bag 325 (**TCF**) is based, at least in part, upon the donor’s **hematocrit** (**HCTD**). In Lavender, both the volume of anticoagulant (**TCF**) and the total plasma filtered (pure plasma) in plasma bag 325 (**TPF**) depend on total plasma flow volume (**TQP**), which is calculated based on the donor’s hematocrit (**HCTD**) via equation $TQP = TQB * (1 - HCTD)$.

156. For example, **TCF** and **TPF** are both calculated based on the total volume of collected dilute plasma (**TDPF**), which is converted from the total dilute plasma filtered weight (**TDPW**), which is the measured total weight of the dilute

plasma collected based on the amount of total plasma flow (**TQP**). **TQP** is a donor-specific amount based on hematocrit (**HCTD**) that determines how much anticoagulant needs to be added to dilute the donor's plasma to 68% of the original plasma concentration. Thus, the values of **TDPW** and **TDPF** change based on **TQP**. EX1004, 22:35-43, 41:4-44:42. Thus, any change in the donor's hematocrit value (**HCTD**) requires a corresponding change in the calculated value of the volume of anticoagulant (**TCF**), and vice versa so the volume of anticoagulant collected in the plasma collection bag (**TCF**) is calculated based, at least in part, on the donor's hematocrit (**HCTD**).

157. Additionally, Lavender calculates the volume of anticoagulant in plasma bag 325 based, at least in part, upon the donor's hematocrit because system 300 uses the plasma bag weight to calculate the volume of anticoagulant in plasma bag 325 (*i.e.*, **total citrate filtered (TCF)**) by multiplying a volume of the total amount of **filtered plasma (TPF)** by conversion factor (**CF**), where **CF** represents the volume of anticoagulant introduced into the incoming whole blood (V_{AC}) per incoming volume of plasma (V_P), or $CF = \frac{V_{AC}}{V_P}$. EX1004, 41:1-44:42 (Table VI, §5(B)). Conversion factor (**CF**) is determined using a predefined ratio of citrate added per milliliter of whole blood to dilute incoming plasma to 68% of the initial concentration. EX1004, 22:35-46.

158. Lavender weighs the collected plasma and anticoagulant solution in plasma bag 325 and transmits the weight to microprocessor 301. EX1004, 16:50-53; 17:14-16. Total plasma in the collected plasma component (**TPF**) is calculated based on the total **volume of anticoagulant** and plasma mixture in the collection container (total dilute plasma filtered (**TDPF**)), which is determined using the collection container's weight. The **TPF** equation is $TPF = TDPF * PDF$. Plasma dilution factor (**PDF**), which represents the ratio of incoming plasma volume (V_P) to the sum of incoming plasma volume and anticoagulant volume (V_{AC}). EX1004, 22:37-39, 41:10-44:57.

159. A POSITA would understand this would be expressed as: $PDF = \frac{V_P}{V_P + V_{AC}}$.

160. Lavender therefore determines the volume of anticoagulant in the collected plasma component, as follows:

$$161. \quad TCF = TPF * CF = TDPF * PDF * CF = TDPF * \left(\frac{V_{AC}}{V_P} \right) * \left(\frac{V_P}{V_P + V_{AC}} \right) = \frac{TDPF * V_{AC}}{V_P + V_{AC}}$$

162. A POSITA would also understand that the volume of plasma introduced into the system (V_P) is related to the volume of whole blood introduced (V_B) as $V_P = V_B * (1 - HCTD)$, which is Lavender's equation for the plasma flow rate ($TQP = TQB * (1 - HCTD)$) converted to a volume equation.

163. Thus, it is my opinion that the equation can also be written as $TCF =$

$\frac{TDPF * V_{AC}}{[V_{AC} + V_B * (1 - HCTD)]}$, showing that Lavender determines the volume of anticoagulant

in the collected plasma from the volume of anticoagulant added to the whole blood and the subject's hematocrit. Therefore, the combination of Lavender, Neyrinck, and Bainbridge discloses this claim because a POSITA would understand that Lavender's volume of anticoagulant is directly calculated based on the donor's hematocrit.

14. **Claim 26: A system according to claim 17, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the number of rotations of the anticoagulant pump.**

164. See §§X.B.7.a-k (claim 17), X.A.5 (claim 5, Ground I).

15. **Claim 28: A system according to claim 17, further comprising: a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma container based, at least in part, on the monitored volume of collected plasma component.**

165. See §§X.B.7.a-k (claim 17), X.A.5 (claim 5, Ground I).

16. **Claim 29: A system according to claim 17, further comprising: a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma container based, at least in part, on the monitored weight of collected plasma component.**

166. See §§X.B.7.a-k(claim 17), X.A.7 (claim 15, Ground I).

C. Ground III: Claim 8 is rendered obvious over Lavender in view of Neyrinck and Darashkevich.

1. Claim 8: A method according to claim 1, wherein the target percentage of plasma is between 26.5 and 29.5 percent of the donor's plasma volume.

167. Lavender calculates a target plasma collection volume that is 18% of the donor's circulating plasma volume. EX1004, 22:39-46.

168. Darashkevich discloses that “[i]n certain embodiments, plasmapheresis will remove between about 15% about 30% of the patient's total circulating plasma.” EX1007, ¶0083.

169. A POSITA would have found it obvious and would have been motivated to combine the Lavender-Neyrinck system with Darashkevich's teachings and would have had a reasonable expectation of success in doing so.

170. A POSITA would have been motivated to specify a percentage of donor's plasma to collect during plasma apheresis and would have turned to, and implemented, Darashkevich's target plasma collection amount—15-30% of donor's plasma volume—in the Lavender-Neyrinck system as all relate to the same well-known plasma apheresis technology. EX1004, 1:12-13, 22:35-46; EX1005, p.39; EX1007, ¶¶0029-30, 0083. Additionally, Lavender calculates a target plasma collection volume that is 18% of donor circulating plasma volume and Darashkevich

discloses removing between about 15% [to] 30% of the patient's total circulating plasma.” EX1004, 22:39-46; EX1007, ¶0083. In view of these disclosures, choosing the target percentage of plasma between 26.5 and 29.5 percent of the donor's plasma volume would have been an obvious design choice, because it is the natural and predictable result of operating within Darashkevich’s disclosed range. EX1007, ¶0083.

171. Further, Lavender recognizes that “various modifications and alterations may be made therein without departing from the true scope and spirit of the present invention.” EX1004, 45:1-7. Thus, it is my opinion that incorporating Darashkevich’s teachings would have been a routine, minor change that would have yielded the predictable result of collecting more plasma. Accordingly, the proposed combination discloses claim 8.

D. Ground IV: Claim 23 is rendered obvious over Lavender in view of Neyrinck, Bainbridge and Darashkevich.

1. Claim 23: A system according to claim 17, wherein the target percentage of plasma is between 26.5 and 29.5 percent of the donor's plasma volume.

172. See §§X.B.7.a-k (claim 17, Ground II), X.C.1 (claim 8, Ground III).

173. As discussed above in §X.B.1, it is my opinion that it would have been obvious to a POSITA to combine Lavender, Neyrinck, and Bainbridge. Additionally, and as discussed with respect to the Lavender, Neyrinck, and

Darashkevich combination, (§X.C.1) a POSITA would have been motivated to modify the Lavender-Neyrinck-Bainbridge system in view of Darashkevich to collect plasma in the range of 15-30% of a donor's plasma volume and would have had a reasonable expectation of success in making the proposed combination because the systems are substantially the same, the modification is minor and routine, and it would have yielded the predictable result of collecting more plasma.

E. Ground V: Claims 10 and 13 are obvious over Lavender in view of Neyrinck and Min

1. Reasons to Combine Lavender, Neyrinck, and Min

174. A POSITA would have found it obvious and would have been motivated to combine Lavender and Neyrinck with Min's use of weigh sensors 246 to track weight changes to more accurately derive fluid processing volumes, including the volume changes of anticoagulant container 276 and plasma collection container 304. EX1008, 11:52-55, 17:17-22.

175. Additionally, a POSITA would have had a reasonable expectation of success in modifying the Lavender-Neyrinck system in view of Min because all relate to the same well-known technologies, all apply substantially similar techniques to achieve similar results, and the functionality of Lavender as modified by Neyrinck would not change when further modified in view of Min—that is, to monitor the weight of an anticoagulant bag during apheresis to determine a change

in volume within the anticoagulant container. EX1008, 11:52-55, 17:17-22.

176. First, Lavender, Neyrinck, and Min are in the same field and all relate to the well-known technologies of separating blood components. EX1004, 1:12-13, 22:35-46; EX1005, p.39; EX1008, 7:51-55. Accordingly, a POSITA would have found it obvious to combine the teachings of Lavender and Neyrinck with Min. Further, combining Lavender, Neyrinck, and Min entails the mere use of known solutions to improve similar systems and methods in the same way, *i.e.*, to use Min's technique of monitoring the weight of an anticoagulant bag to determine a volume of anticoagulant provided to whole blood prior to separation of blood components.

177. Second, Lavender, Neyrinck, and Min apply substantially similar techniques to achieve similar results. As discussed above, Lavender discloses fractionating blood "to **collect blood substances, such as plasma.**" EX1004, 1:12-13. Similarly, Neyrinck discloses separating plasma from a donor's blood cells and storing it in a plasma collection bag. EX1005, p.39. Further, Min discloses a system for "separating whole blood into plasma and red blood cells." EX1008, 4:26-29. It is known to a POSITA that the transfer volume of peristaltic pumps depends mainly on their loaded tube segment. *See, e.g.*, EX1007, pp.83-87. The transfer volume of peristaltic pumps can differ by $\pm 10\%$ than expected due to manufacturing deviations. EX1007, pp.83-87. This deviance can cause significant error. EX1007, pp.83-87. Therefore, a POSITA would have been motivated to add Min's weigh sensors into

Lavender's blood fractionating system to gather and generate more detailed information for maximizing processing and separation efficiencies and reduce potential errors in determining the volume of anticoagulant due to errors in the blood and anticoagulant pump rates (*e.g.*, errors in pumps 306, 308 in Lavender). EX1004, Fig. 20; EX1008, 1:37-42, 11:52-55, 17:17-22.

178. Also, Min's systems for determining the amount of anticoagulant added to a blood separation system are similar to Lavender's monitoring of the added anticoagulant. Indeed, Min's anticoagulant container and tube arrangement (*See* Fig. 10) is structurally similar to Lavender's (*See* Fig. 20). EX1008, 3:26-29. Therefore, it is my opinion that it would have been obvious, and a POSITA would have been motivated, to modify Lavender's blood fractionating system to incorporate Min's weigh sensors. Additionally, it would have been an obvious design choice as it would have provided a more accurate anticoagulant volume amount and, in turn, lead to calculating a more accurate pure plasma volume.

179. Finally, the intended functionality of Lavender's blood fractionating system would not change by adding Min's weigh sensors as a POSITA would have expected Lavender's blood fractionating system to successfully determine the amount of anticoagulant added to the system when modified in view of Min.

180. Lavender also discloses converting weight changes to volume changes using a specific gravity. Accordingly, a POSITA would have had a reasonable

expectation of success when modifying Lavender's algorithms for determining the volume of anticoagulant in the collected plasma component to incorporate Min's scale for monitoring the anticoagulant volume's weight change—each relate to the same well-known technologies and apply substantially similar techniques to achieve similar results.

2. **Claim 10: A method according to claim 1, further comprising: determining a change in volume within an anticoagulant container, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the change in volume within the anticoagulant container.**

181. Lavender in view of Neyrinck and Min discloses determining a change in volume within an anticoagulant container, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the change in volume within the anticoagulant container. As the '416 patent recognizes, it is my opinion that a POSITA would understand that substantially all of the anticoagulant added to a centrifuge-based blood fractionating system would end up in the plasma collection container. See §VIII.B; EX1001, 10:67-11:4. As discussed above, it would have been obvious for a POSITA to replace Lavender's membrane-based fractionator with Min's centrifuge-based blood processing chamber 18. EX1004, 6:3-12; EX1008, 7:41-59. It was generally known in the art that a centrifuge-based blood separation device, provided comparable treatment faster than a membrane-

based blood separation device. See EX1012, p.135. A POSITA would have been motivated to modify Lavender with Min's centrifuge-based collection device to separate plasma from a donor's blood more quickly.

182. A POSITA would have had a reasonable expectation of success in making this modification as Min's centrifuge-based blood processing device is used for the same purpose as Lavender's system—separating whole blood into plasma—and implementing the centrifuge-based device in Lavender would have been a simple substitution that would have resulted in faster plasma separation and collection.

183. In the combined Lavender-Neyrinck-Min blood fractionating system, a POSITA would understand that the plasma collection container would contain substantially all of the added anticoagulant.

184. Further, as discussed above, it would have been obvious to a POSITA to incorporate Min's scale in Lavender/Neyrinck's system to monitor the change in volume of the anticoagulant container and calculate the volume of anticoagulant in the collected plasma component based, at least in part, on the change in volume within the anticoagulant container. It is my opinion that doing so would generate more detailed information for maximizing processing and separation efficiencies and reduce potential errors in determining the volume of anticoagulant due to errors in the blood and anticoagulant pump rates (*e.g.*, errors in pumps 306, 308 in

Lavender). EX1004, Fig. 20; EX1008, 1:37-42.

3. Claim 13: A method according to claim 1, wherein the volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

185. The volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn whole blood. Lavender uses an anticoagulant pump in system 300 for pumping anticoagulant into the donor's whole blood before separating blood components. EX1004, 15:47-53, 16:54-17:2, claim 1, Figs. 1, 20. At least a portion of the anticoagulant introduced in the withdrawn whole blood is collected in the plasma collection bag because anticoagulant is pumped "at a rate sufficient to dilute incoming plasma to 68% of the initial concentration." EX1004, 22:37-39.

186. The volume of anticoagulant in the collected plasma component also includes at least a portion of the anticoagulant added during a priming step. Lavender discloses a priming step, *e.g.*, "[t]he citrate bag 307 is then unclamped, and the system operates the citrate pump 306 to drive citrate to purge air from the tubes 312 and 314 [of system 300]." EX1004, 20:37-48. Min discloses that during the priming step, "anticoagulant pump PP4 conveys a predetermined volume of anticoagulant (*e.g.*, 10g) into the in-process container 312" where plasma is collected. EX1008, 22:40-42. Thus, it is my opinion that at least a portion of the volume of anticoagulant

in the collected plasma component (*e.g.*, plasma bag 325) would include at least a portion of the anticoagulant added during the priming step.

187. A POSITA would have been motivated to combine Lavender and Neyrinck's teachings with Min for the same reasons as discussed above. §X.E.1. Additionally, it is my opinion that a POSITA would have looked to Min to calculate the total collection volume, including the volume of anticoagulant added during priming, to reduce errors caused by not accounting for all added anticoagulant when determining the anticoagulant volume in the plasma collection container.

F. Ground VI: Claim 25 is obvious over Lavender in view of Neyrinck, Bainbridge and Min.

- 1. Claim 25: A system according to claim 17, further comprising: an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant source based on the measured weight of the anticoagulant source, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the change in volume within the anticoagulant source.**

188. *See* §X.E.1.

189. As discussed in §X.B.1, it is my opinion that it would have been obvious to a POSITA to combine Lavender, Neyrinck, and Bainbridge, and a POSITA would have had a reasonable expectation of success in combining them. Additionally, and like with the combination of Lavender, Neyrinck, and Min, in

§X.F.1, a POSITA would have been motivated to modify the Lavender-Neyrinck-Bainbridge system in view of Min to track weight changes to more accurately derive fluid processing volumes, including the volume change of the anticoagulant and plasma collection containers. EX1008, 11:52-55, 17:17-22. Similarly, a POSITA would have had a reasonable expectation of success in making the proposed combination because the systems are substantially the same, the modification is minor and routine, and would have yielded predictable results.

190. Lavender discloses a controller that monitors the change in volume within a collection container by converting a change in weight to a change in volume using specific gravity. §X.E.1. Min uses weigh sensors 246 to track the anticoagulant container's weight changes and derive fluid processing volumes, including the volume change of anticoagulant container 276 and plasma collection container 304. EX1008, 11:52-55, 17:17-22. Each of Min's weigh sensors "provide output reflecting weight changes over time" and "[t]his output is conveyed to [a] controller. . . [for] process[ing] the incremental weight changes to derive fluid processing volumes." EX1008, 17:17-22. Thus, the combined system discloses an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source (*i.e.*, Min's weigh sensors), and the controller further configured to monitor a change in volume within the anticoagulant source based on the measured weight of the anticoagulant source (*i.e.*, Min's controller). EX1008, 17:17-22. As discussed above,

a POSITA would understand that substantially all of the anticoagulant added to Lavender's blood fractionating system, when modified to include Min's centrifuge-based device, would end up in the plasma collection container and that a POSITA would incorporate Min's monitoring of the anticoagulant source's volume into Lavender's algorithms to provide additional measurements of the anticoagulant volume in the plasma collection container. *See* §§VIII.B, X.E.1; EX1001, 10:67-11:4; EX1004, 43:28; EX1008, 17:17-22. Thus, Lavender in view of Neyrinck, Bainbridge, and Min teaches the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the change in volume within the anticoagulant source.

G. Ground VII: Claim 12 is obvious over Lavender in view of Neyrinck, Min, and Turgut

- 1. Claim 12: A method according to claim 1, further comprising: determining a volume of anticoagulant within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device.**

191. Lavender calculates a volume of anticoagulant collected in the collected plasma component by weighing the collected plasma and anticoagulant solution in plasma bag 325. EX1004, 16:50-53, 17:14-16; *See* §X.A.2.j. Min uses weigh sensors 246 to track the anticoagulant container's weight changes and derive fluid processing volumes, including the volume change of anticoagulant container 276

and plasma collection container 304. EX1008, 11:52-55, 17:17-22. However, a POSITA would have recognized that determining the total volume of anticoagulant in the collected plasma component based on the anticoagulant container's change in volume would not account for any anticoagulant remaining in the blood separation device. *See* §X.E.1. A POSITA would have also recognized that the anticoagulant volume in the plasma collection container would be more accurately determined if the anticoagulant remaining in the blood separation device was accounted for.

192. A POSITA would have found it obvious and would have been motivated to combine Lavender, Neyrinck, and Min with Turgut's teaching of a volume detector—a centrifuge separation chamber used to separate blood into components—to determine the volume of fluid within a blood separation system. EX1009, ¶0073.

193. A POSITA would have found it obvious to combine the teachings of Lavender, Neyrinck and Min with Turgut because they are in the same field of endeavor with the same well-known technologies of separating blood components.

194. Turgut's blood component separation system is structurally similar to Lavender's (*See* Fig. 20) and is used to separate blood into different components. EX1009, ¶¶0052-68, Fig. 1A. Therefore, it would have been obvious, and a POSITA would have been motivated, to modify the Lavender-Min blood fractionating system, which monitors the anticoagulant volume input into the system and includes

Min's centrifuge (see §X.E.1), to incorporate Turgut's volume detector to detect the fluid volume (plasma plus anticoagulant) remaining in the blood separation device.

195. A POSITA would have used Turgut's volume detector to determine the volume of fluid in the separation device and then have subtracted the volume of red blood cells (total volume of whole blood times hematocrit (**HCTD**)) to calculate the volume of anticoagulant and plasma in the device. A POSITA would then multiply this volume times the plasma dilution factor times the conversion factor (*i.e.*, $PDF * CF$) to calculate the volume of anticoagulant remaining within the blood component separation device. This remaining anticoagulant volume would then be subtracted from the amount of anticoagulant added to the system to more accurately estimate the total amount of anticoagulant within the plasma collection container.

196. It is my opinion that the combined system discloses determining a volume of anticoagulant within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device.

H. Ground VIII: Claim 27 is obvious over Lavender in view of Neyrinck, Bainbridge, Min, and Turgut

- 1. Claim 27: A system according to claim 17, further comprising: an optical sensor located on the blood**

component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device.

197. See §X.G.1 (claim 12, Ground VII).

198. As discussed above in §X.F.1, it would have been obvious to a POSITA to combine Lavender, Neyrinck, Bainbridge, and Min, and a POSITA would have had a reasonable expectation of success in doing so. Additionally, and as discussed with respect to the Lavender, Neyrinck, Min, and Turgut combination, (§IX.G.1) a POSITA would have been motivated to modify the Lavender-Neyrinck-Bainbridge-Min system in view of Turgut to use a volume detector to more accurately calculate the volume of anticoagulant within the plasma collection container by accounting for anticoagulant remaining in the blood separation device. EX1009, ¶0073. Similarly, a POSITA would have had a reasonable expectation of success in making the proposed combination because the systems are substantially the same, the modification was minor and routine, and it would have yielded predictable results.

199. It is my opinion that a POSITA would recognize that Turgut's volume detector may be an optical sensor, like Headley's optical sensor, discussed below. EX1010, 1:10-24; 4:48-64. See §§X.I.1-2. It was generally known by a POSITA at the time of the '416 patent's effective filing date that a volume detector may be an

optical sensor.

I. Ground IX: Claims 16 and 30 are obvious over Lavender in view of Neyrinck, Bainbridge, Headley, and Barrett

- 1. Claim 16: A method according to claim 1, wherein step (b) includes monitoring a volume of red blood cells collected within the blood component separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the donor.**

200. Lavender teaches determining a volume of whole blood withdrawn from the donor in the Main Loop algorithm, which calculates the total blood flow (TQB) as blood is withdrawn. EX1004, 43:7-16. Lavender's blood pump and citrate pump rates are based on the donor's hematocrit. EX1004, 41:21-26.

201. Bainbridge teaches separating red blood cells from incoming whole blood during a blood separation procedure. EX1006, ¶0087. Headley relates to systems and methods for separating platelets and other blood components from blood. EX1010, Abstract. Headley teaches using an array 97 of optical sensors within a blood separation system (*e.g.*, a centrifuge) to determine a volume of red blood cells within the blood separation system. EX1010, 1:10-24; 4:48-64. It would have been obvious for a POSITA to include Headley's optical sensor(s) in Lavender's blood separation device to determine the volume of red blood cells collected from the donor and allow for their immediate return to the donor.

202. Barrett teaches determining a donor's hematocrit by dividing a blood sample's red blood cell volume by the sample's total volume. EX1011, 2:45-49.

203. A POSITA would have been motivated to combine the teachings of Lavender, Neyrinck, Bainbridge, Headley with Barrett, each of which relate to blood-component separation and use similar systems, to determine a real-time hematocrit of a donor during a collection procedure. EX1004, 22:35-46; EX1006, ¶0086-87; EX1010, 1:10-24; 4:48-64; EX1011, 2:45-49.

204. A POSITA would have been motivated to incorporate Barrett's teaching of determining a donor's hematocrit by dividing the total red blood cell volume of a blood sample over the total volume of a blood sample to determine the donor's hematocrit as blood is being drawn from the donor to reduce error in Lavender's calculated values. For example, Lavender's pump rates, which are determined based on the donor's hematocrit, would be more accurately regulated with real-time hematocrit updates. EX1004, 41:21-26.

205. Thus, a POSITA would use both (i) Headley's monitored volume of red blood cells and (ii) the volume of whole blood withdrawn from the donor, Lavender's total blood flow (**TQB**), to determine a donor's real-time hematocrit. This equation would be added into Lavender's Main Loop algorithm to increase the accuracy of Lavender's calculated estimates. Also, to more effectively separate the red blood cells in Lavender's system, a POSITA would be motivated to replace

Lavender's membrane-based blood fractionator with Bainbridge's centrifuge-type blood processing vessel to separate the blood into blood components. §X.E.1 and 3; EX1004, 6:3-12; EX1006, ¶0086-87.

206. It would have been an obvious design choice to use Barrett's equation in the modified system of Lavender to determine the real-time hematocrit of the donor during a separation procedure. Further, the intended functionality of the Lavender-Neyrinck-Bainbridge system would not change when modified to include Headley's optical sensor(s) and Barrett's hematocrit calculation. That is, a POSITA would have expected the combined system to successfully determine the hematocrit of a donor using a red blood cell volume determined by Headley's optical sensor(s) and Barrett's equation for hematocrit.

207. Accordingly, it is my opinion that Lavender in view of Neyrinck, Bainbridge, Headley, and Barrett teach monitoring a volume of red blood cells collected within the blood component separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the donor. EX1004, 41:8-44:32; EX1006, ¶0087; EX1010, 1:10-24; 2:45-49; 4:48-64, 17:19-24; EX1011, 2:45-49. For example, applying Barrett's equation would determine the hematocrit of a donor by dividing the red blood cell volume of a blood sample (*e.g.*, the volume of red blood cells collected)

by the total volume of the blood sample (*e.g.*, total blood flow into the system, Lavender's TQB). EX1004, 41:8-44:32; EX1006, ¶0087; EX1010, 1:10-24; 2:45-49; 4:48-64

2. **Claim 30: A system according to claim 17, further comprising: an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood component separation device, the controller configured to determine the donor's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the donor.**

208. See §X.I.1 (Claim 16).

209. As discussed above, Headley teaches using an array 97 of optical sensors within a blood separation system (*e.g.*, a centrifuge) to determine a volume of red blood cells within the blood separation system. EX1010, 1:10-24; 4:48-64. Thus, Headley discloses an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood component separation device. See §X.I.1; EX1010, 1:10-24; 4:48-64.

210. Accordingly, Lavender in view of Neyrinkc, Bainbridge, Headley, and Barrett teaches an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood component separation device using Headley's optical sensor. EX1010, 4:48-64.

211. It is my opinion that using Lavender's Main Loop algorithm, Headley's

optical sensor, and Barrett's equation to determine hematocrit, Lavender, modified in view of Neyrinck, Bainbridge, Barrett, and Headley teaches an optical sensor configured to monitor a volume of red blood cells and a controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the subject. See §X.I.1; EX1004, 41:8-44:32; EX1006, ¶0087; EX1010, 2:45-49.

XI. Availability for Cross-Examination

212. In signing this declaration, I recognize that the declaration will be filed as evidence in a 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 the time allotted for cross examination.

XII. Right to Supplement

213. I reserve the right to supplement my opinions in the future to respond to any arguments that the Patent Owner may raise and to take into account new information as it becomes available to me.

XIII. Jurat

214. I declare that all statements made herein of my own knowledge are true

Declaration of Dr. Gary Fletcher in Support of Petition for
Inter Partes Review of U.S. Patent No. 10,792,416
IPR2025-01420

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:	Respectfully submitted,
October 8, 2025 <hr/>	 Gary D. Fletcher, Ph.D.