

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TERUMO BCT INC.,

Petitioner

v.

HAEMONETICS CORP.,

Patent Owner

IPR2026-00045

U.S. Patent No. 10,980,934

**DECLARATION OF GARY D. FLETCHER, PH.D. IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO.
10,980,934**

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EXHIBIT LIST

Exhibit	Reference
1001	U.S. Patent No. 10,792,934 (“’934 patent”)
1002	File History of the ’934 patent
1004	U.S. Patent No. 4,898,675 (“Lavender”)
1005	“Calculations in Apheresis” (“Neyrinck”)
1006	U.S. Patent No. 7,072,769 (“Fletcher-Haynes”)
1007	U.S. Patent Publication No. 2011/0097344 (“Darashkevich”)
1008	“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.
1009	“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.
1010	Bruce C. McLeod, MD, et al., “Apheresis: Principles and Practice,” 3rd Edition, AABB Press 2010.
1011	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
1012	Japanese Patent Publication No. JP 2002-282352 A and certified Japanese to English translation (“Takagi”)
1013	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. 10,980,934 (“’934 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 ’934 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 '934 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 EX1013 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 EX1013.

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

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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

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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 EX1013.

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 ’934 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 '934 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 '934 Patent (EX1001), the prosecution history (EX1002) of the '934 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 No. 7,072,769, issued July 4, 2006 (“Fletcher-Haynes,” EX1006);
- U.S. Patent Publication No. 2011/0097344, published April 28, 2011 (“Darashkevich,” EX1007);
- “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. (EX1008);
- “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. (EX1009);
- Bruce C. McLeod, MD, et al., “Apheresis: Principles and Practice,” 3rd Edition, AABB Press 2010. (EX1010);
- 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>
(EX1011); and

- Japanese Patent Publication No. JP 2002-282352 A and English translation (“Takagi,” EX1008)

16. I have considered these materials through the lens of a POSITA, which is discussed further in §§V and VI (below) related to the '934 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, 5, 6, 23-27, and 30 are obvious over Lavender in view of Neyrinck;
- Claims 2-4, 8-13, 15-22, 28, and 29 are obvious over Lavender in view of Neyrinck, and Fletcher-Haynes;
- Claim 7 is obvious over Lavender in view of Neyrinck, and Darashkevich;
- Claim 14 is obvious over Lavender in view of Neyrinck, Fletcher-Haynes, and Darashkevich;

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.

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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 '934 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. EX1010, Chapter 1: Development of Apheresis Instrumentation. It selectively removes plasma and returns cellular components along with replacement fluid using centrifugation or membrane filtration. EX1011. 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. EX1010, 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. EX1009. 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. EX1009.

35. At the time the '934 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. EX1010, 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. EX1010, 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 '934 patent. *See, e.g.*, EX1012.

VIII. '934 Patent Overview

A. The '934 Patent is Related to Plasma Apheresis

36. The '934 patent, which I understand issued on April 20, 2021, 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* EX1010, 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.*, EX1010, 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, 1:24-27. The '934 patent specifically relates to plasma apheresis, which is plasma collection. Figure 3 of the '934 patent shows one embodiment of a plasma apheresis system.

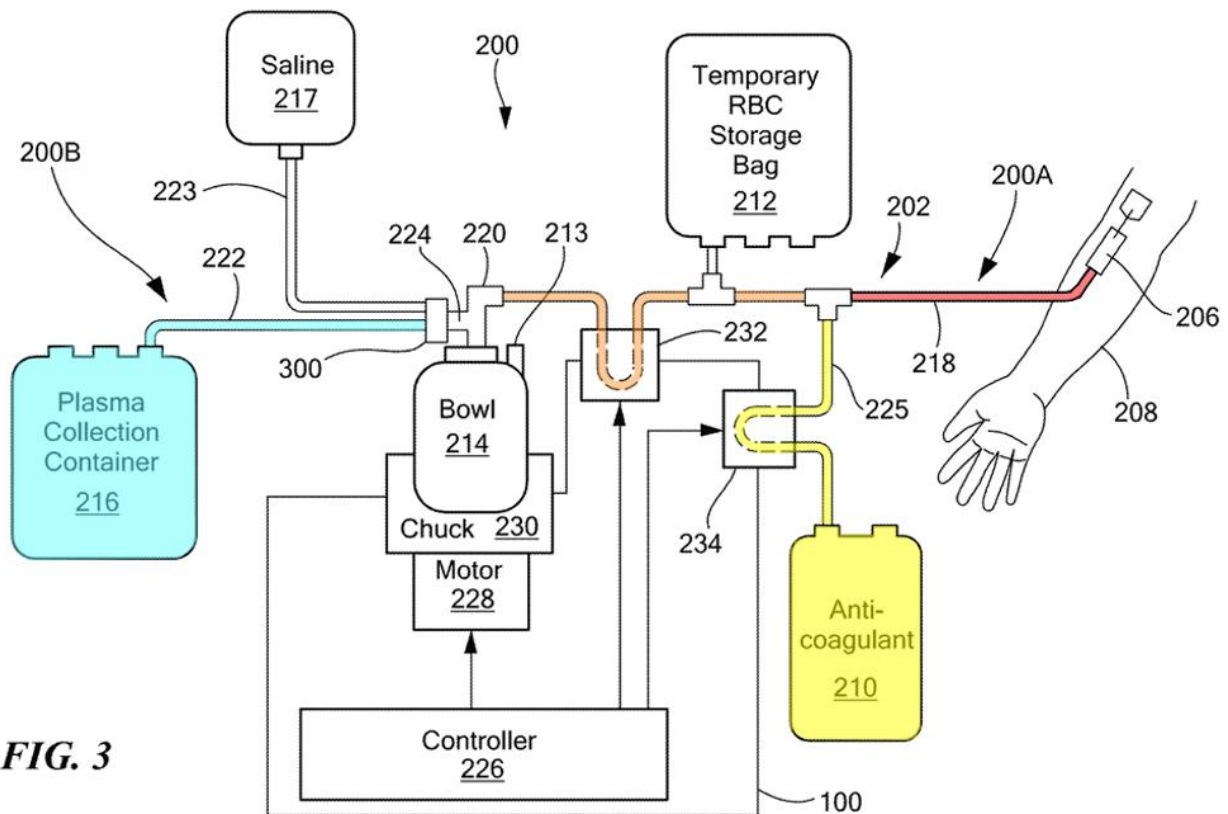


FIG. 3

EX1001, Fig. 3 (annotated).

37. Plasma apheresis involves withdrawing whole blood from a donor using venous access device 206. EX1001, 8:1-6. 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, 8:24-26, 8:67-9:5.

Anticoagulant is introduced in fixed proportions to the whole blood drawn from the donor to prevent blood clotting in the draw line. *See* EX1009. “[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, 10:34-46.

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, 7:39-7:49, 9:25-35. 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, 4:12-19, 8:1-8:13. The anticoagulant and pure plasma combination is known as anticoagulated plasma or plasma product. EX1001, 12:44-45.

39. The FDA established guidelines regarding how much plasma any individual donor can donate. *See* EX1009. These guidelines consider donor parameters, like weight, hematocrit, and sex. *See* EX1009.

B. The ’934 Patent’s Purported Invention

40. The ’934 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, 1:51-56, 1:66-2:24, 6:60-7:6.

41. Each donor has a different hematocrit level, which affects the amount of plasma in the donor's whole blood. EX1001, 10:43-46. The differing levels of hematocrit affect the volume of anticoagulant in a plasma collection bag ("anticoagulant volume"). EX1001, 10:51-54. Given this variability, the '934 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, 13:50-54. 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, 10:64-11:33. 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, 10:64-11:33. Anticoagulated whole blood is extracted blood mixed with anticoagulant.

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

42. The '934 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, 10:2-4, 10:37-41. 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, 10:55-11:51. The '934 patent first calculates the anticoagulant volume. EX1001, 11:34-51. 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, 11:34-51.

43. The '934 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, 11:16-51. 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, 11:5-10. 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 11:5-10, 12:9-27. In both these methods disclosed in the '934 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, 11:5-11:10, 11:16-33, 12:13-27.

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, 12:55-58.

45. In the '934 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, 12:66-13:3. 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, 11:56-62.

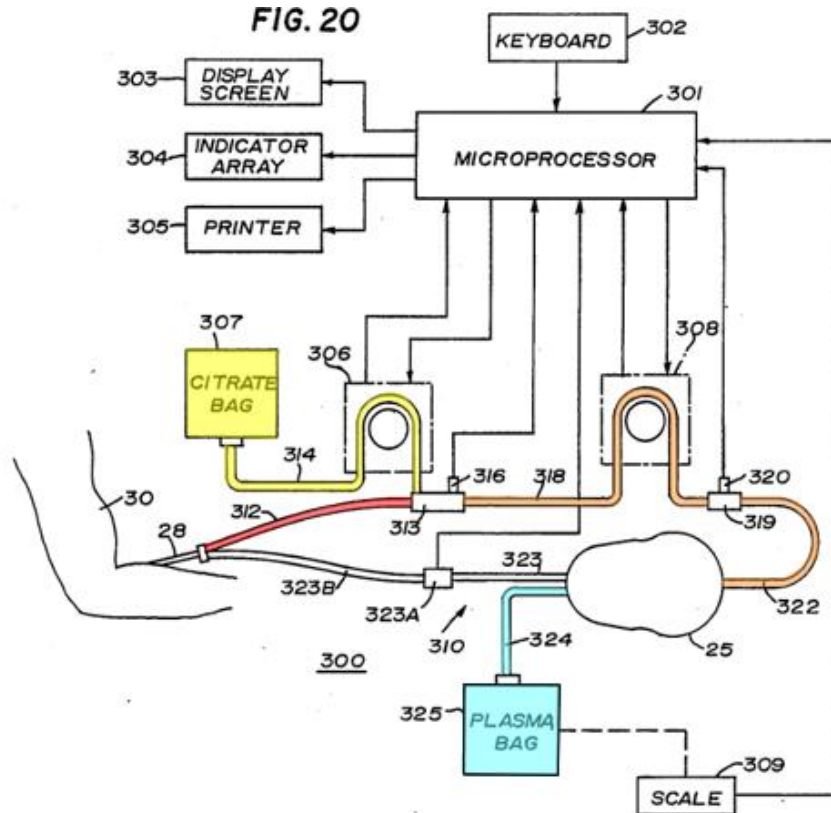
46. As I will explain below, these concepts were well known as of the priority date of the '934 patent.

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.

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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
<i>CF</i> (conversion factor)	Predetermined ratio (or percentage) of anticoagulant to incoming plasma
<i>PDF</i>	Plasma dilution factor
<i>C1</i>	ml plasma collected/pound of <i>BW</i>
<i>C2</i>	ml dilute plasma collected/pound of <i>BW</i>
<i>C3</i>	ml citrate to be filtered/pound of <i>BW</i>
<i>QB</i>	Blood flow from donor
<i>TQB</i>	Total blood flow
<i>HCTD</i>	Donor’s hematocrit

<i>BW</i>	Donor's body weight
<i>QP</i>	Plasma flow
<i>TQP</i>	Total plasma flow
<i>QC</i>	Citrate flow
<i>QCP</i>	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
<i>MAXPF</i>	Total plasma filtered (pure plasma) volume to collect
<i>MAXCF</i>	Total citrate (i.e. anticoagulant) volume to collect
<i>MAXDPF</i>	Total dilute plasma to collect (mixture of plasma and anticoagulant)

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 Fletcher-Haynes

58. Fletcher-Haynes discloses a blood collection system that maximizes blood component yield by maximizing at least one process parameter, based on either a target yield or a fixed procedure time. EX1006, Abstract. Fletcher-Haynes recognized the need to determine a target amount of pure plasma to collect for a donor “considering the medical and physical characteristics of the donor.” EX1006, 48:29-31; 52:13. For example, Fletcher-Haynes’ prediction algorithms include a donor’s gender, height, weight, hematocrit, and platelet pre-count parameters. EX1006, 27:30-35; 49:19-52:36.

59. Figure 7A illustrates Fletcher-Haynes’ collection assembly 10’ for separating blood into components. EX1006, 45:14-16. Donor’s blood is pumped through inlet line 22 (red), and anticoagulant is pumped from AC container 30 (yellow) into to the inlet line 22. EX1006, 45:22-37. Blood component separation device 18 separates anticoagulated whole blood into separate components flowing into platelet collect bags 38 and plasma collect bag 54. EX1006, 45:22-37. The remaining, uncollected blood is pumped back to the donor using return line 46. EX1006, 45:22-37.

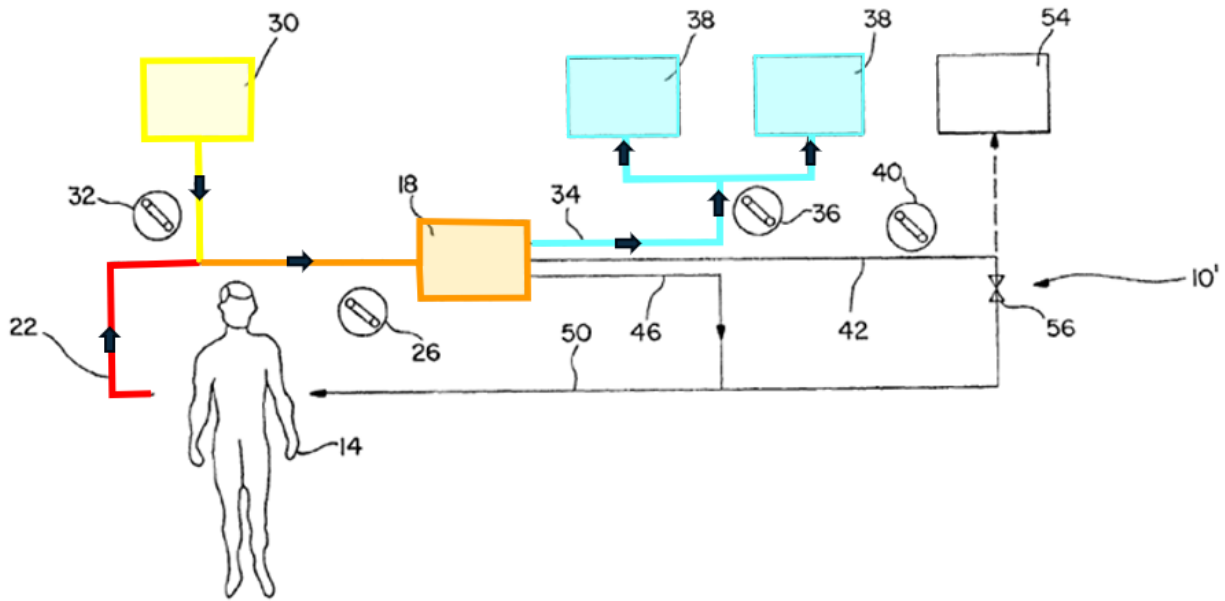


Figure 7A

EX1006, Fig. 7A (annotated).

60. Fletcher-Haynes' prediction model uses an initial parameter configuration that accounts for these factors (i.e., height, weight, total blood volume, hematocrit, and platelet pre-count) to generate several target parameters, including: ". . . ; (2) inlet flow rate; (3) AC ratio; (4) procedure time; . . . ; (7) source plasma volume; (8) AC in the platelet and plasma collect bags 38, 54; . . . ; (10) AC infusion rate; and (11) output approval." EX1006, 49:22-26. When executed prior to a blood separation procedure, the prediction model determines target values of any of parameters (1)-(11). EX1006, 34:8-24; 48:66-49:19-25; EX1003, ¶60. When

executed during a blood separation procedure, the prediction model determines any of parameters (1)-(11) in real-time. EX1006, 34:8-24; 48:66-49:19-25.

61. Fletcher-Haynes' prediction algorithms may be integrated with its optimization algorithms, and Fletcher-Haynes specifically recites "the optimizer model 172 may interface with the prediction model or actually integrally incorporate the prediction model," and refers to Eqs. 1-22. EX1006, 58:63-67. Stated differently, Fletcher-Haynes discloses 22 equations that can be incorporated into a prediction model to predict a particular blood component's yield. EX1006, 58:63-67. One is an equation for calculating total blood volume using a donor's height and weight, another is an equation for calculating anticoagulant (AC) ratio using a donor's hematocrit, another is an equation for the total volume in the source plasma bag or a target volume of diluted plasma (i.e. plasma and anticoagulant mixture) using the anticoagulant (AC) ratio, and another is an equation for calculating source plasma volume or a target pure plasma volume collected or to collect. EX1006, 49:40-52:17. Specifically, Equation 10 defines the total blood volume of a donor (V_B) using a donor's height and weight; Equation 9 defines the AC Ratio (R) using a donor's hematocrit; Equation 22 defines the total volume in the source plasma bag or total volume of diluted plasma (V_{SPB}), and Equation 17 defines the predicted total volume of pure plasma in the source plasma bag (V_{SP}). EX1006, 49:40-52:17. These

equations can be integrated with Fletcher-Haynes' optimization algorithms.
EX1006, 58:63-67.

62. Fletcher-Haynes explains that it is preferable during procedures "to have computer/database system 140 exert control over apheresis machine functions, including process control manipulation and optimization." EX1006, 34:8-24, 49:40-52:17. Because computer/database system 140 can control apheresis machine functions, including process control manipulation and optimization, a POSITA would understand that optimizer and prediction models, and any of equations 1-22, would be executed prior to or during those procedures. EX1006, 34:8-24, 49:40-52:17.

D. Overview of Darashkevich

63. 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.

X. Identification of How the '934 Patent's Claims are Unpatentable

A. Ground I: Claims 1, 5, 6, 23-27, and 30 are rendered obvious over Lavender in view of Neyrinck

1. Reasons to Combine Lavender and Neyrinck

64. In my opinion, a POSITA would have found it obvious and would have been motivated to combine Lavender's system and Neyrinck's teachings and would have had a reasonable expectation of success in doing so because 1) both relate to the same well-known technologies, 2) both apply substantially similar techniques to achieve similar results, and 3) Lavender's intended functionality would remain substantially the same in the proposed combination.

65. 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.

66. 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.

67. 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.

68. 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.

69. 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, *e.g.*, weight. 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 been motivated to combine Lavender and Neyrinck and would have had a reasonable expectation of success in doing so.

2. Claim 1

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

70. 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 the weight and height of a donor;

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

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

73. 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 the hematocrit of the donor;

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

75. 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;

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

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

78. 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.

79. 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 volume to collect based, at least in part, on the calculated donor plasma volume and a target percentage of plasma;**

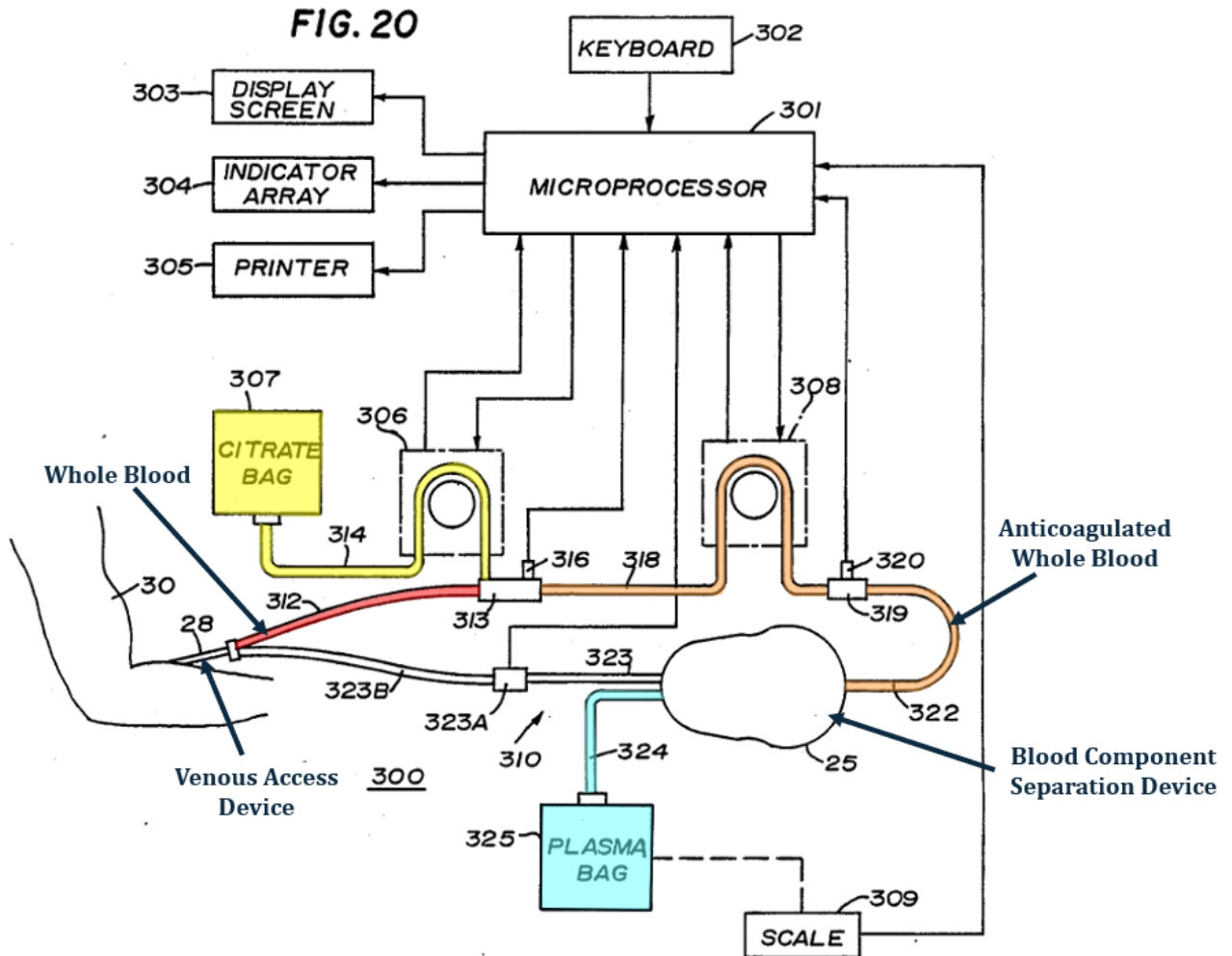
80. Lavender calculates a target plasma collection volume that is 18% of a donor's circulating plasma volume. EX1004, 22:39-46. Additionally, the Main Loop of the algorithm in Table VI repeats until a desired amount of plasma has been collected, such as the determined target pure plasma collection volume (*MAXPF*).³ EX1004, 21:62-22:2. Thus, Lavender's *MAXPF* is a target plasma volume. EX1004, 21:62-22:2. It is my opinion that the target plasma 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 a venous-access device and a first line, the first line connected to a blood component separation device;**

³ All emphasis added unless otherwise noted.

81. 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, 5:44.

82. 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.

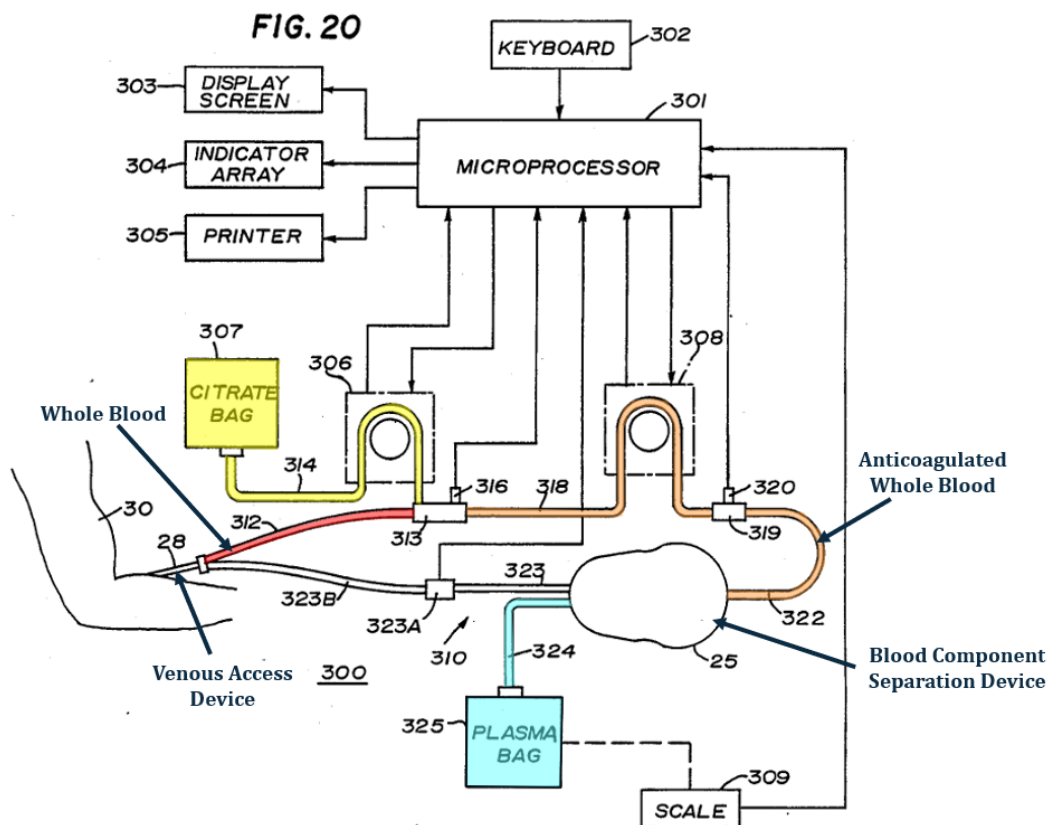
83. Blood fractionator 25 is a blood component separation device because

“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;

84. 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;

85. 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;

86. 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] continuing steps (e) through (h) until the target plasma volume to collect is reached in the plasma collection container.

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

88. 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 5: 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.

89. Lavender in view of Neyrinck renders obvious claim 5.

90. 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.

91. 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.

92. 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***

⁴ All emphasis added unless otherwise noted.

based on BMI) into Lavender's system to improve collection accuracy and donor safety.

4. Claim 6: A method according to claim 1, wherein the target plasma volume to collect is calculated before withdrawing whole blood.

93. Lavender calculates the target volume of plasma to collect when the system algorithm is initialized. Before withdrawing the whole blood, Lavender's system initializes the system algorithm of Table VI. EX1004, 20:55-68, 41:1-44:33, Figs. 25A-25D. This includes steps 2 and 3 set forth in Table VI, which relate to placing predetermined constants into the system algorithm and calculating pump rates for the blood and anticoagulant pumps. EX1004, 20:55-59, 41:4-44:42, Table VI, §2.g. This timing is also described in Message 43 in Table V that is displayed on Lavender's display as "PLEASE WAIT FOR A FEW MOMENTS" while "variables are initialized." EX1004, 35:37-40. When the internal calculations are finished, Message 44 is displayed instructing the user to insert a needle into the donor's vein to start withdrawing whole blood. EX1004, 35:35-45.

5. Claim 23

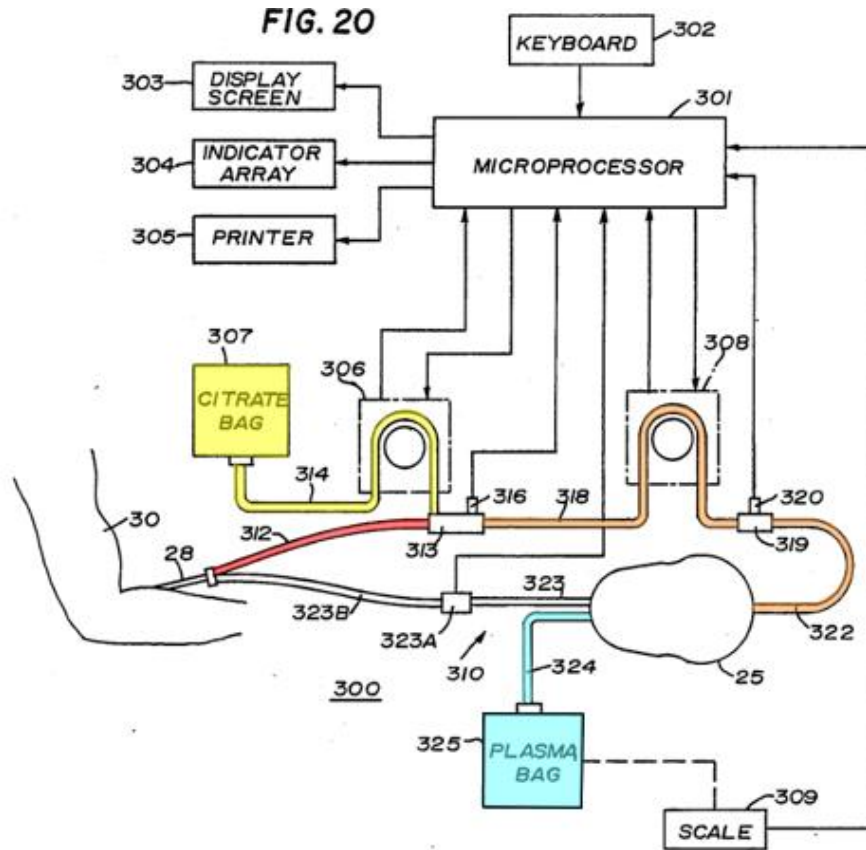
a. 23[preamble] A system for collecting plasma comprising:

94. *See* §X.A.2.a (1[preamble]).

b. 23[a] a blood processing device including:

95. Lavender's system 300 is a blood processing device. EX1004, 16:34-

53.



EX1004, Fig. 20 (annotated).

- c. **23[b] a venous-access device for drawing whole blood from a donor and returning blood components to the donor,**

96. See §X.A.2.f(1[e]).

- d. **23[c] 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 collection container,**

97. *See* §§X.A.2.f, X.A.2.h-i (1[e], 1[g], 1[h]).

- e. **23[d] a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump, and**

98. *See* §X.A.2.f (1[e]).

- f. **23[e] an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and**

99. *See* §X.A.2.g (1[f]).

- g. **23[f] a controller configured to (1) calculate a donor plasma volume based, at least in part, on the weight and height of the donor and the hematocrit of the donor,**

100. *See* §X.A.2.d (1[c]).

101. 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. Microprocessor 301 is part of the blood processing device (*e.g.*, system 300). *See* EX1004, Fig. 20.

- h. 23[g] (2) calculate a target plasma volume to collect based, at least in part, on the calculated donor plasma volume and a target percentage of plasma, and**

102. See §X.A.2.e (1[d]).

- i. 23[h] (3) calculate a target collection volume based, at least in part, on the calculated target plasma volume to collect.**

103. See §X.A.2.e (1[d]).

104. Lavender teaches a target collection volume that is a target pure plasma collection volume to collect (*MAXPF*) in the plasma collection container.

See §X.A.2.e; EX1004, 21:62-22:2.

- 6. Claim 24: The system according to claim 23, wherein the blood processing device is configured to stop the blood draw pump when the target collection volume is collected within the plasma collection container.**

105. See §X.A.2.j (1[i]).

106. Lavender discloses that when the desired amount of plasma, such as the determined target pure plasma collection volume (*MAXPF*), has been collected, the program stops the pumps and displays "End-Message" indicating that the plasma collection is complete. EX1004, 21:62-22:6; 41:1-44:33 (Table VI, §5.C); Fig. 25D.

- 7. Claim 25: The system according to claim 23, wherein the controller is part of the blood processing device.**

107. 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. Microprocessor 301 is part of the blood processing device (*e.g.*, system 300). *See* EX1004, Fig. 20.

8. Claim 26: The system according to 23, wherein the controller is further configured to program the blood processing device with a blood processing end point based, at least in part, on the target collection volume.

108. *See* §§X.A.2.e, j (1[d], 1[i]).

109. The Main Loop of the algorithm in Table VI repeats until a desired amount of plasma has been collected, such as the determined target pure plasma collection volume (*MAXPF*). EX1004, 21:62-22:2. Thus, the point at which the algorithm in the Main Loop does not repeat and stops the pumps to display "End-Message" is the blood processing end point that is based on the target collection volume. EX1004, 21:62-22:2.

9. Claim 27: A system according to claim 26, wherein the blood processing end point is when the target collection volume has been collected within the plasma collection container.

110. *See* §X.A.8 (Claim 26).

111. Lavender discloses stopping the pumps and displaying “End-Message” when a desired amount of plasma, such as the determined target pure plasma collection volume (*MAXPF*), has been collected. EX1004, 21:62-22:2, 41:1-44:33 (Table VI, §5.C); Fig. 25D. Thus, it is my opinion that the point at which the target pure plasma volume (*MAXPF*) has been collected is the blood processing end point. EX1004, 21:62-22:2.

10. Claim 30: A system according to claim 23, 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 based, at least in part, on the donor's body mass index.

112. *See* §§X.A.3, 5 (Claim 5, claim 23).

B. Ground II: Claims 2-4, 8-13, 15-22, 28, and 29 are rendered obvious over Lavender in view of Neyrinck and further in view of Fletcher-Haynes.

1. It would have been obvious to combine the Lavender-Neyrinck system with Fletcher-Haynes.

113. As discussed above in §X.A.1 (Ground I), it is my opinion that a POSITA would have been motivated to combine Lavender’s system with Neyrinck. Additionally, a POSITA would have been motivated to combine the Lavender and Neyrinck system with Fletcher-Haynes 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 Fletcher-Haynes.

114. A POSITA would have been motivated to combine the Lavender and Neyrinck system with Fletcher-Haynes to optimize plasma collection yield.

EX1006, 54:52-58. Lavender discloses a membrane-based blood fractionator.

EX1004, 6:3-12. Fletcher-Haynes discloses a blood apheresis system including a single needle and a single donor access line 62 to draw and return the donor's blood. EX1006, 45:58-46:5, Fig. 7B. Donor access line 62 is connected to blood component collection device 18 to separate blood into various blood components (*e.g.*, platelets, plasma, red blood cells). EX1006, EX1006, 45:58-46:5, Fig. 7B.

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. Fletcher-Haynes' system draws a donor's blood into a centrifuge-type blood component collection device to separate the blood into blood component types (*e.g.*, plasma, red blood cells). EX1006, 45:58-46:5; 46:16-29. 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* EX1008, p.135. Therefore, it is my opinion that a POSITA would have been motivated to modify the Lavender and Neyrinck system in view of Fletcher-

Haynes's centrifuge-based collection device to more efficiently separate plasma from a donor's blood and reduce the overall procedure time.

116. Additionally, it is my opinion that a POSITA would readily implement any of Fletcher-Haynes' calculations into the Lavender and Neyrinck system to optimize determining target volumes. A POSITA would also incorporate any of Fletcher-Haynes' calculations into Lavender's system to optimize the data tracking and donor parameter monitoring before, during, and after a blood draw procedure.

117. In my opinion, a POSITA would have been motivated to combine the teachings of the Lavender and Neyrinck system with Fletcher-Haynes' teachings, and would have had a reasonable expectation of success, because, for example, and as discussed above, each relate to the same well-known technologies. Additionally, both apply substantially similar techniques to achieve similar results and the Lavender and Neyrinck system's functionality would not change in the combination as Fletcher-Haynes is used for the same purpose as the Lavender and Neyrinck system—using donor parameters to determine the total amount of pure plasma to collect.

118. The intended functionality of the Lavender and Neyrinck system's blood component collection device would not change when implementing Fletcher-Haynes' calculations because Fletcher-Haynes' calculations would simply

replace or be incorporated into the parameters calculated in Table VI of Lavender's algorithm. Additionally, both seek to optimize collecting blood components, like plasma, from a donor. That is, a POSITA would have expected the Lavender and Neyrinck system's blood component collection device to successfully determine a target amount of anticoagulant to collect and/or a target amount of pure plasma to collect like in Fletcher-Haynes.

119. Additionally, it is my opinion that incorporating Fletcher-Haynes' equations into the Lavender and Neyrinck system would have been a routine, minor change to the system that would have yielded predictable results, as a POSITA would have understood that Fletcher-Haynes' algorithms are essentially the same as Lavender's algorithms. For example, a POSITA would have understood Fletcher-Haynes' anticoagulant volume expressed as a fraction of pure plasma volume (f_{ACP}) is equivalent to Lavender's conversion factor (CF) for ml of citrate per ml of plasma.

120. As a second example, Fletcher-Haynes' Equation 15 further defines $f_{ACP} = [(R - 1) * (1 - H)]^{-1}$. R is defined in Equation 3 as $\frac{Q_{IN}}{Q_{AC}}$, which is the ratio of flow of anticoagulated whole blood to flow of anticoagulant. In my opinion, a POSITA would understand that in Lavender $R = \frac{(Q_B + Q_C)}{Q_C} = \frac{Q_B}{Q_C} + 1$, so that $\frac{Q_B}{Q_C} = R - 1$. Lavender's equation TABLE VI, 2.a states that $\frac{Q_P}{Q_B} = 1 - HCTD$.

Hence a POSITA would understand from Lavender's equation 2.b. that $CF =$

$$\frac{QC}{QP} = \frac{QC}{QB} * \frac{QB}{QP} = \frac{1}{(R-1)} * \frac{1}{(1-HCTD)} \text{ or } CF = [(R - 1) * (1 - HCTD)]^{-1}, \text{ which}$$

is the same equation as Fletcher-Haynes f_{ACP} . As a third example, it is my opinion that a POSITA would understand that the sum of Lavender's total plasma filtered (TPF) and total citrate filtered (TCF) is equal to Lavender's total dilute plasma filtered; $TDPF = TPF + TCF = TPF + TPF * CF = TPF * (1 + CF)$, or $TDPF = TPF * (1 + CF)$. Similarly, Lavender's $MAXDPF = MAXPF + MAXCF = MAXPF * (1 + CF)$, which is equivalent to Fletcher-Haynes' Eq. 22.

121. In my opinion, incorporating Fletcher-Haynes' algorithms into the Lavender and Neyrinck system would have been a known software modification that would have yielded predictable results. That is, incorporating Fletcher-Haynes' algorithms into Lavender's Main Loop entails the mere use of similar equations to improve similar systems and methods in the same way.

122. Thus, it is my opinion that a POSITA would have been motivated to make, and would have had a reasonable expectation of success in making, these proposed modifications to the Lavender and Neyrinck system in view of Fletcher-Haynes' disclosures because, for example, Fletcher-Haynes' disclosed calculations for target plasma volume can be implemented using minor software modifications in Lavender's main loop algorithm (*e.g.*, as $MAXPF$ in Table VI).

2. **Claim 2: A method according to claim 1, further comprising: calculating a volume of anticoagulant to be collected with the plasma component in the plasma collection container, the volume of anticoagulant to be collected with the plasma component based, at least in part, on the hematocrit of the donor.**

123. Lavender in view of Neyrinck and Fletcher-Haynes renders obvious claim 2.

124. Lavender calculates a volume of anticoagulant to be collected in the collected plasma component. Specifically, Lavender's system determines the total volume of citrate, an anticoagulant, to collect (*MAXCF*) before starting a procedure. EX1004, 20:46-54, 41:1-44:33 (Table VI, §2(i)). *MAXCF* is determined by multiplying the donor's bodyweight (*BW*) by a predetermined constant (*C3*), which is also derived from a predetermined ratio of plasma to anticoagulant used to dilute incoming plasma to 68%, i.e. $C3 = C1 * CF$. EX1004, 22:35-41, 41:4-44:42. While the donor's hematocrit is not explicitly used to determine *MAXCF*, the Lavender and Neyrinck system determines the donor's hematocrit. EX1004, 20:10-14; EX1005, pp. 39-40, Fig. 3..

125. Fletcher-Haynes' system also determines the donor's hematocrit. EX1006, 20:9-15. Further, Fletcher-Haynes' system discloses, via a prediction model, calculating a volume of anticoagulant to be collected with a plasma component in a plasma collection container based, at least in part, on the donor's

hematocrit. EX1006, 48:49-65; 50:49-50, 50:61, 51:12-14. In my opinion, a POSITA would use Fletcher-Haynes' f_{ACP} and V_{SPB} equations in Lavender's Table VI calculations to determine a $MAXCF$ value because doing so would allow Lavender to directly use hematocrit to determine $MAXCF$, resulting in a more accurate determination of the anticoagulant volume to collect during the plasma collection process.

126. Specifically, Fletcher-Haynes determines the fraction of AC in the collected plasma component f_{ACP} using an AC ratio and the donor's hematocrit in equation 15.

$$f_{ACP} = [(R - 1)(1 - H)]^{-1}$$

127. R is the ratio of the collective flow of anticoagulant and blood through the inlet line in relation to the flow of anticoagulant through the inlet line, and H is the donor's hematocrit. EX1006, 48:21-32, 50:16-52:14.

128. Equation 17 defines a predicted or target source plasma volume, *i.e.*, the maximum volume of pure plasma to collect in the collection container. EX1006, 48:54-62, 50:16-52:14. Equation 22 recites:

$$V_{SPB} = V_{SP}(1 + f_{ACP})$$

where V_{SPB} is the total volume in the source plasma bag (including plasma and anticoagulant), V_{SP} is the volume of pure plasma in the source plasma bag.

EX1006, 50:16-52:14. When the f_{ACP} equation is inserted into the V_{SPB} equation, it

is clear that V_{SPB} is based on a donor's hematocrit:

$$V_{SPB} = V_{SP}(1 + [(R - 1)(H - 1)]^{-1})$$

129. In my opinion, a POSITA would look to Fletcher-Haynes' equations using hematocrit to determine target volumes in Lavender's system to better determine the volume of anticoagulant to be collected. Specifically, a POSITA would look to incorporate Fletcher-Haynes' Equations 15, 17, and 22 to determine Lavender's *MAXCF* based on the donor's hematocrit. As will be discussed below, a POSITA would recognize the following variables are equivalent in Lavender and Fletcher-Haynes:

Lavender's Variable	Fletcher-Haynes' Variable	Definition
<i>MAXPF</i>	V_{SP}	The target amount of pure plasma to collect in the collection container
<i>MAXDPF</i>	V_{SPB}	The target amount of dilute plasma (plasma and anticoagulant mixture) to collect in the collection container

130. In my opinion, a POSITA would have been motivated to plug Lavender's *MAXPF* into Fletcher-Haynes' equations to solve for a *new MAXCF* that is based on the donor's hematocrit, as doing so should provide a more accurate

result.

131. In my opinion, a POSITA would understand that Lavender's *MAXPF*, which, as shown above is equivalent to V_{SP} , would be used in Fletcher-Haynes' Equation 22 to determine V_{SPB} , the target total volume of dilute plasma to be collected in a plasma collection bag, as shown in the below equations (showing substituted Equation 22 and with the expanded f_{ACP} equation):

$$V_{SPB} = MAXPF(1 + f_{ACP})$$

$$V_{SPB} = MAXPF(1 + [(R - 1)(H - 1)]^{-1})$$

132. In my opinion, a POSITA would also recognize that the target anticoagulant volume in the collection container may be determined by subtracting the target pure plasma volume from the target dilute plasma volume (e.g. $MAXCF = V_{SPB} - MAXPF$) because only plasma and anticoagulant are collected in the plasma collection container. *See* EX1006, 23:39-41. The determined V_{SPB} using Lavender's *MAXPF* would then be used to determine a target volume of anticoagulant to be collected within the plasma collection bag, or *new MAXCF*, by subtracting *MAXPF* from V_{SPB} :

$$new\ MAXCF = V_{SPB} - MAXPF$$

133. The *new MAXCF* calculated using Fletcher-Haynes' equations would replace Lavender's *MAXCF*, resulting in a more accurate anticoagulant target

volume. Below is the *new MAXCF* equation with the above-derived equation for

V_{SPB} plugged in:

$$\text{new MAXCF} = (\text{MAXPF}(1 + [(R - 1)(H - 1)]^{-1})) - \text{MAXPF}$$

or

$$\begin{aligned}\text{new MAXCF} &= \text{MAXPF}([(R - 1)(H - 1)]^{-1}) \\ &= \text{MAXPF} * f_{ACP}\end{aligned}$$

134. In other words, the *new MAXCF* equation shown above utilizes equations 15, 17, and 22 from Fletcher-Haynes, and a POSITA would simply solve for *new MAXCF* using Fletcher-Haynes' equations to determine *new MAXCF* using both the donor's weight and hematocrit. In my opinion, a POSITA would easily recognize that R is defined in Equation 3 of Fletcher-Haynes as $\frac{Q_{IN}}{Q_{AC}}$, which is the ratio of flow of anticoagulated whole blood to flow of anticoagulant, which are variables already calculated in Lavender (e.g., Q_B and Q_C). A POSITA would understand that in Lavender $R = \frac{(Q_B + Q_C)}{Q_C} = \frac{Q_B}{Q_C} + 1$. This R may be used in the *new MAXCF* equation shown above.

135. In my opinion, this *new MAXCF* would replace Lavender's original *MAXCF*, and include a donor's hematocrit. Because V_{SPB} is determined using f_{ACP} , and f_{ACP} is based on the donor's hematocrit, this series of equations determines a target volume of anticoagulant to be collected within the plasma collection bag

directly based on the donor's hematocrit.

3. Claim 3: A method according to claim 2, wherein the target plasma volume to collect is a target volume of pure plasma to collect plus the calculated volume of anticoagulant to be collected.

136. Lavender in view of Neyrinck and Fletcher-Haynes renders obvious claim 3.

137. Lavender's system monitors the total volume of dilute plasma (*TDPF*), a mixture of pure plasma and anticoagulant, collected during a procedure by measuring the weight of the plasma collection container with a scale and converting the weight using a specific gravity constant (*SGDP*). EX1004, 16:50-53, Table VI §§1.g., 1.i., and 5.B. Additionally, Lavender's system calculates the total dilute plasma to collect (*MAXDPF*), which would include both pure plasma and anticoagulant. EX1004, 16:50-53, Table VI §2.i.

138. In my opinion, a POSITA would be motivated to set a target collection volume of dilute plasma compared to a target collection volume of pure plasma in Lavender's system to provide additional options to a user. For example, the FDA established guidelines regarding how much plasma any individual donor can donate which provides a maximum plasma volume to collect and a maximum dilute plasma volume (*i.e.*, plasma and anticoagulant) to collect for specific donor weight ranges. *See* EX1009. To allow a user to select between these options for

target collection volumes, a POSITA would be motivated to modify Lavender's main loop algorithm to set a target collection volume as a target dilute plasma volume instead of a target pure plasma volume.

139. Furthermore, Fletcher-Haynes defines a target collect volume (V_{SPB}), which is equivalent to the total dilute plasma volume ($MAXDPF$), as a target volume of dilute plasma for a procedure. *See* EX1006, 23:39-41; 48:32-65; 51:10-12; 52:14. Specifically, Fletcher-Haynes discusses establishing a plasma volume limit and defines plasma volume as "the volume of plasma collected during a procedure (plasma product volume plus anticoagulant volume)." *See* EX1006, 23:39-41; 48:32-65; 51:10-12; 52:14. Thus, it is my opinion that a POSITA would be motivated to modify the Main Loop algorithm, specifically §5.C. of Table VI, in Lavender to compare $TDPF$ with $MAXDPF$ and stop the main loop algorithm when $TDPF$ is equal to or greater than $MAXDPF$, setting the target collection volume to $MAXDPF$, the target volume of diluted plasma to collect. In my opinion, a POSITA would readily understand that $MAXDPF$ is equal to *new* $MAXCF$ plus $MAXPF$.

4. **Claim 4: A method according to claim 2, wherein the target plasma volume to collect is a target volume of pure plasma to collect in the plasma collection container, the target volume of pure plasma to collect based, at least in part, upon the volume of anticoagulant to be collected with the plasma component in the plasma collection container.**

140. Lavender discloses a target plasma volume to collect that is a target pure plasma collection volume to collect (*MAXPF*) in the plasma collection container. *See* §X.A.2.e; EX1004, 21:62-22:2.

141. Additionally, as discussed above, it is my opinion that it would have been obvious to a POSITA in view of Lavender, Neyrinck, and Fletcher-Haynes to determine a volume of anticoagulant to be collected with a plasma component in a plasma collection container based, at least in part on the hematocrit of the donor. *See* §§X.B.2.

142. As described in §X.B.2, it is my opinion that a POSITA would be motivated to incorporate Fletcher-Haynes' calculations into Lavender's system to more accurately determine a target volume of pure plasma. *See* §X.B.2. Further, after updating Lavender's *MAXCF* with *new MAXCF*, a POSITA would recognize the need to also update *MAXPF* to more accurately account for the total volume of fluid (*MAXDPF*) in the plasma collection container.

143. Lavender's *MAXDPF* is the total volume of fluid to collect in the plasma collection container, consisting of a mixture of pure plasma and anticoagulant. Lavender's *MAXDPF* is determined based on the donor's weight and a predetermined constant, $MAXDPF = BW * C2$. In my opinion, the predetermined constant *C2* is derived from a predetermined ratio of plasma to anticoagulant used to dilute incoming plasma by 68% of its initial concentration,

i.e., $C2 = C1 / PDF$. EX1004, 22:35-43. As discussed above, it is my opinion that a POSITA would recognize that only plasma and anticoagulant are collected in the plasma collection container, and thus the determined *new MAXCF* plus the determined *MAXPF* should equal the determined *MAXDPF* (*e.g.*, $MAXDPF = MAXCF + MAXPF$). See EX1006, 23:39-41.

144. In my opinion, a POSITA would understand that updating *MAXPF* would be accomplished by subtracting the *new MAXCF* (determined based on the donor's hematocrit) from the *MAXDPF* (determined based on the donor's weight) (*e.g.* $new MAXPF = MAXDPF - new MAXCF$). See §X.B.2; EX1004, 22:35-41, 41:4-44:42. When a POSITA utilizes Fletcher-Haynes' calculations in Lavender's system, a target volume of pure plasma may be determined based on a donor's hematocrit or *new MAXPF* as described above. See §X.A.2.d-e; EX1004, 22:35-41, 41:4-44:42. The equation for *new MAXPF* utilizes the donor's hematocrit through the calculation of *new MAXCF*.

145. In my opinion, it would have been obvious to a POSITA to set this *new MAXPF* as a target collection volume in Lavender, and thus determine a target collection volume based on this *new MAXPF*. See §X.B.2, EX1004, Table VI, §5.C. By determining the target collection volume this way, the *new MAXCF* based on the donor's hematocrit is used to determine the target collection volume

(i.e. *new MAXPF*), which increases the number of donor characteristics used to determine the target collection volume compared to the *MAXPF*, or target pure plasma volume, determined in Lavender. A POSITA would recognize that using *new MAXPF* as a target collection volume would result in a more accurate and patient specific target plasma volume.

146. In my opinion, by calculating the *new MAXPF* as the target collection volume, a POSITA would be utilizing both the calculated volume of anticoagulant and the calculated volume of pure plasma because *new MAXPF* is the calculated volume of pure plasma that is determined using the calculated volume of anticoagulant (i.e. *new MAXCF*). *See* §X.B.2.

5. Claim 8

a. 8[preamble] A system for collecting plasma comprising:

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

b. 8[a] a venous-access device for drawing whole blood from a donor and returning blood components to the donor;

148. *See* §X.A.2.f (1[e], Ground I).

c. 8[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 collection container;

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

- d. **8[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;**

150. See §X.A.2.f (1[e], Ground I).

151. Lavender in view of Neyrinck and Fletcher-Haynes renders obvious the limitations of claim element 8[c].

152. 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.

153. Fletcher-Haynes discloses a blood apheresis system including a **single needle and a single donor access line** 62 to return the donor's blood after collecting plasma from a donor. EX1006, 45:58-46:5, Fig. 7B.

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

- e. **8[d] an anticoagulant line connected to an anticoagulant source, the anticoagulant line**

configured to introduce anticoagulant into the drawn whole blood; and

155. *See* §X.A.2.g (1[f], Ground I).

- f. 8[e] a controller configured to control the operation of the blood component separation device and the first pump,**

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

157. 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. 8[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,**

158. *See* §X.A.2.d (1[c], Ground I).

- h. 8[g] (2) a target plasma volume to collect based, at least in part, on the calculated donor plasma volume and a target percentage of plasma,**

159. *See* §X.A.2.e (1[d], Ground I).

- i. **8[h] (3) a volume of plasma component collected within the plasma collection container,**

160. *See* §X.A.2.i (1[h], Ground I).

- j. **8[j] the controller configured to stop the first pump when the calculated volume of plasma component collected within the plasma collection container equals the target plasma volume to collect.**

161. *See* §X.A.2.j (1[i], Ground I).

162. Lavender discloses that when the desired amount of plasma has been collected, the program stops the pumps and displays "End-Message" indicating that the plasma collection is complete. EX1004, 21:62-22:6.

- 6. **Claim 9: A system according to claim 8, wherein the controller is further configured to calculate a volume of anticoagulant to be collected with the plasma component in the plasma collection container, the volume of anticoagulant to be collected with the plasma component based, at least in part, on the hematocrit of the donor.**

163. *See* §§X.B.5.a-j, X.B.2 (claims 2, 8).

- 7. **Claim 10: A system according to claim 9, wherein the target plasma volume to collect is a target volume of pure plasma to collect plus the calculated volume of anticoagulant to be collected.**

164. *See* §§X.B.6, X.B.3 (claims 3, 9).

- 8. **Claim 11: A system according to claim 9, wherein the target plasma volume to collect is a target volume of pure plasma to collect within the plasma collection container, the target volume of pure plasma to collect based, at least in part, upon the volume of anticoagulant to be collected with the plasma component in the plasma collection container, the**

controller configured to stop the first pump when the volume of pure plasma collected within the plasma collection container equals the target plasma collection volume.

165. See §§X.B.6, X.B.4 (claims 4, 9).

9. Claim 12: A system according to claim 8, 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.

166. See §§X.B.5.a-j (claim 8), X.A.3 (claim 5, Ground I).

10. Claim 13: A system according to claim 8, wherein the target plasma volume to collect is calculated before withdrawing whole blood.

167. See §§X.B.5.a-j (claim 8), X.A.4 (claim 6, Ground I).

11. Claim 15

a. 15[preamble] A method for programming a blood processing device comprising:

168. Lavender discloses a method for programming a blood component processing device (e.g., “automated system 300 including a blood fractionating system 20”). EX1004, 16:34-53, 18:53-20:68, Figs. 25A-25C. Microprocessor 301 of system 300 operates under stored program control, and the program is menu-driven with the menu messages appearing on a display screen 303, with “various display messages which appear during the operation of the program, the possible user replies and the response of the system 300 to these replies are all set forth in

Table V.” EX1004, 18:53-62, Table V, Fig. 20. Microprocessor 301 is

programmed to control automated system 300 including blood fractionating system

20. EX1004, 18:53-62, Table V, Fig. 20.

b. 15[a] receiving, in a control system, a weight and height of a donor;

169. Lavender’s system, and specifically Lavender’s “control system” (e.g. microprocessor 301, keyboard 302, display screen 303, indicator array 304), receives a weight of the donor through “entry and validation of donor data, including ... donor weight in pounds.” EX1004, 20:10-14; *see* also EX1004, Abstract. The system’s program displays messages 32-36, which direct the user in entry and validation of donor data, including . . . , donor weight in pounds. . . ” EX1004, 20:10-14.

```
MESSAGE 35
***** User enters donor weight and
* presses ENTER.
* ENTER DONOR WEIGHT IN LBS: * Value checked for upper and lower
* acceptable limits. If out of range
* GOTO Low_weight_error or High_weight_error.
***** If value okay GOTO Message 36.
```

EX1004, Table V, Message 35.

170. The “controller” is used throughout the claims of the ’934 patent, and Lavender’s microprocessor 301 may correspond to the “controller” in the ’934 patent claims. EX1004, 16:34-17:28, 18:53-21:27, Fig. 20. Also, the “control system” is used throughout the claims of the ’934 patent, and Lavender’s system

300, and specifically display screen 303, indicator array 304, printer 305, keyboard 302, and microprocessor 301 together may correspond to the “control system” in the ’934 patent claims. EX1004, 16:34-17:28, 18:53-21:27, Fig. 20.

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

172. 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. 15[b] receiving, in a control system, a hematocrit of the donor;

173. Lavender’s system, and specifically Lavender’s “control system” (microprocessor 301), receives a hematocrit of the donor through “entry and validation of donor data, including ... donor hematocrit.” EX1004, 20:10-14; see also EX1004, Abstract. EX1003, ¶148. The system’s program displays messages 32-36, which direct the user in entry and validation of donor data, including . . . , donor hematocrit. . .” EX1004, 20:10-14, Abstract.

```
MESSAGE 34
*****
* User enters donor's hematocrit value.
* When ENTER pressed check value for
* ENTER DONOR HEMATOCRIT (PER CENT): * lower limits of male and female.
* If less than 38 and female GOTO Crit_error_female.
* If less than 41 and male GOTO Crit_error_male.
*****
* If value okay GOTO Message 35.
```

EX1004, Table V, Message 34.

- d. **15[c] calculating, using the control system, a donor plasma volume, the control system calculating the donor plasma volume based, at least in part, on the weight and height of the donor and the hematocrit of the donor;**

174. *See* §X.A.2.d (1[c]).

175. System 300's microprocessor 301 calculates and executes the algorithms detailed in Table VI of Lavender. EX1004, 18:53-56.

- e. **15[d] calculating, using the control system, a target plasma volume to collect, the control system calculating the target plasma volume to collect based, at least in part, on the calculated donor plasma volume and a target percentage of plasma;**

176. *See* §X.A.2.e (1[d]).

- f. **15[e] determining a target collection volume based, at least in part, on the calculated target plasma volume to collect; and**

177. *See* §X.A.2.e (1[d]).

178. Lavender teaches a target collection volume that is a target pure plasma collection volume to collect (*MAXPF*) in the plasma collection container.

See §X.A.2.e. EX1004, 21:62-22:2.

- g. **15[f] programming a controller of a blood processing device with a blood processing end point, the blood processing end point being based, at least in part, on the target collection volume.**

179. *See* §§X.A.2.e, j (1[d], 1[i]).

180. The Main Loop of the algorithm in Table VI repeats until a desired amount of plasma has been collected, such as the determined target pure plasma collection volume (*MAXPF*). EX1004, 21:62-22:2. Thus, the point at which the algorithm in the Main Loop does not repeat for stopping the pumps and displaying "End-Message" is the blood processing end point that is based on the target collection volume. EX1004, 21:62-22:2.

12. Claim 16: A method according to claim 15, further comprising: calculating, using the control system, a volume of anticoagulant to be collected with a plasma component in a plasma collection container, the control system calculating the volume of anticoagulant to be collected with the plasma component based, at least in part, on the hematocrit of the donor.

181. See §§X.B.2, 11.a-g (Claims 2, 15).

13. Claim 17: A method according to claim 16, wherein the target plasma volume to collect is a target volume of pure plasma to collect, the target volume of pure plasma to collect based, at least in part, upon the volume of anticoagulant to be collected with the plasma component.

182. See §X.B.4, 12 (Claim 4, 16).

14. Claim 18: A method according to claim 17, wherein the target collection volume is the target volume of pure plasma to collect.

183. See §§X.B.13 (Claim 17), §X.A.2.e (1[d], Ground I).

184. Lavender teaches a target collection volume that is a target pure plasma collection volume to collect (*MAXPF*) in the plasma collection container.

See §X.A.2.e. EX1004, 21:62-22:2.

15. Claim 19: A method according to claim 17, wherein the target collection volume is the target volume of pure plasma to collect plus the calculated volume of anticoagulant to be collected in the plasma collection container.

185. See §§X.B.3, 4, 14 (Claim 3, 4, 17).

16. Claim 20: A method according to claim 15, further comprising: calculating, using the control system, the donor's body mass index based, at least in part on the weight and height of the donor, the control system calculating the donor plasma volume based, at least in part, on the donor's body mass index.

186. See §§X.B.11.a-g (claim 15), X.A.3 (claim 5, Ground I).

17. Claim 21: A method according to claim 15, wherein the blood processing end point is when the target collection volume has been collected within a plasma collection container of the blood processing device.

187. See §§X.B.11.a-g (claim 15), X.A.8 (claim 26).

18. Claim 22: A method according to claim 15, wherein the control system includes the controller.

188. See §X.B.11.b.

189. Lavender's "control system" includes microprocessor 301, keyboard 302, display screen 303, indicator array 304, and potentially other components shown in Fig. 20 or otherwise described. EX1004, 20:10-14. A POSITA would recognize that microprocessor 301 is equivalent to a controller.

19. Claim 28: A system according to claim 23, wherein the target plasma volume to collect is a target volume of pure

plasma to collect in the plasma collection container, the target volume of pure plasma to collect based, at least in part, upon a volume of anticoagulant to be collected with the plasma component in the plasma collection container.

190. *See* §§X.A.5 (claim 23, Ground I), X.B.4 (claim 4).

20. Claim 29: A system according to claim 28, wherein the target collection volume is the target volume of pure plasma to collect and/or the target volume of pure plasma to collect plus the volume of anticoagulant to be collected in the plasma container.

191. *See* §§X.B.3, 4, 19 (Claim 3, 4, 28).

C. Ground III: Claim 7 is rendered obvious over Lavender in view of Neyrinck and Darashkevich.

1. Claim 7: 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.

192. Lavender calculates a target plasma collection volume that is 18% of the donor's circulating plasma volume. *See* §X.A.1.e; EX1004, 22:39-46.

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

194. In my opinion, 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.

195. In my opinion, 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. EX1004, 22:39-46; EX1007, ¶0083.

196. 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. EX1003, ¶171. Accordingly, the proposed combination discloses claim 8.

D. Ground IV: Claim 14 is rendered obvious over Lavender in view of Neyrinck, Fletcher-Haynes, and Darashkevich.

1. Claim 14: A system according to claim 8, wherein the target percentage of plasma is between 26.5 and 29.5 percent of the donor's plasma volume.

197. See §§X.B.5.a-j (claim 8, Ground II), X.C.1 (claim 7, Ground III).

198. 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 Fletcher-Haynes. 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-Fletcher-Haynes 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.

XI. Availability for Cross-Examination


199. 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

200. 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

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

Dated:	Respectfully submitted,
October 24, 2025	 Gary D. Fletcher, Ph.D.