UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TERUMO BCT INC.,

Petitioner

v.

HAEMONETICS CORP.,

Patent Owner

PGR2026-00006

U.S. Patent No. 12,377,204

DECLARATION OF GARY D. FLETCHER, PH.D. IN SUPPORT OF PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 12,377,204

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EXHIBIT LIST

Exhibit	Reference
1001	U.S. Patent No. 12,377,204 ("'204 Patent")
1002	File History of the '204 Patent
1004	U.S. Patent No. 4,898,675 ("Lavender")
1005	U.S. Patent No. 7,072,769 ("Fletcher-Haynes")
1006	"Calculations in Apheresis" ("Neyrinck")
1007	"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.
1008	Curriculum Vitae ("CV") of Dr. Gary D. Fletcher
1009	Bruce C. McLeod, MD, et al., "Apheresis: Principles and Practice," 3rd Edition, AABB Press 2010.
1010	Japanese Patent Publication No. JP 2002-282352 A and certified Japanese to English translation ("Takagi")
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

Terumo BCT, the "Petitioner," requests post grant review of claims 1-30 of U.S. Patent No. 12,377,204 (the "'204 Patent") (EX1001).

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 a post grant review ("PGR") proceeding of U.S. Patent No. 12,377,204 ("the '204 patent," EX. 1001).

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 '204 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 PGR, *inter partes* review, or other proceeding involving the ’204 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 EX1008 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 EX1008.

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

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

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

11. As an R&D director at Becton Dickinson ("BD") from 2004 to 2014, I developed blood collection and blood separation devices for diagnostic testing. I led a 5-member technology development group executing technology strategy to support medical device blood specimen collection and preservation business. I led research and development resolving manufacturing problems in core plastic blood collection products, and initiated a technology development stage-gate process to reduce technology risk in new product development. I also completed a "deep dive" technology assessment in blood fractionation technologies, leveraging and contacting academic experts in materials and fluidics, and led development effort assessing primary blood separation technologies. I also led product development in new business spaces, including the point of care blood collection and diagnostic testing space.

12. I have experience with the U.S. Patent system. I am co-inventor on fifteen issued U.S. Patents and ten issued European patents for devices and methods in the area of blood collection and processing including lancing devices and blood separation for diagnostic testing. A complete list of my patents is set forth in my curriculum vitae, attached hereto as EX1008.

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 '204 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 '204 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 '204 Patent (EX1001), the prosecution history (EX1002) of the '204 Patent, and the following materials:

- U.S. Patent No. 4,898,675 to Lavender ("Lavender," EX1004);
- U.S. Patent No. 7,072,769 to Fletcher-Haynes *et al.* ("Fletcher-Haynes," EX1005);
- "Calculations in Apheresis" ("Neyrinck," EX1006)
- "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. (EX1007)
- Bruce C. McLeod, MD, et al., "Apheresis: Principles and Practice," 3rd Edition, AABB Press 2010. (EX1009)
- Japanese Patent Publication No. JP 2002-282352 A and English translation ("Takagi," 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)

16. I have considered these materials through the lens of a POSITA, which is discussed further in §§V and VI (below) related to the '204 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 8, 11-15, 17-20, 23-24, and 27-29 are anticipated by Fletcher-Haynes alone;
- Claims 1, 3-7, 9, 21-22, 25, and 30 are obvious over Fletcher-Haynes in view of Lavender;
- Claims 10, 16, and 26 are obvious over Fletcher-Haynes in view of Neyrinck;
- Claim 2 is obvious over Fletcher-Haynes in view of Lavender and further in view of Neyrinck;
- Claims 3, 6, 12, 14, 19-20, and 28-29 lack an adequate written description;
- Claims 3, 8, 12, 20, 23, and 29 are indefinite; and
- Claims 3, 12, 20, and 29 are not enabled.

V. LEGAL PRINCIPLES

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

A. Claim Construction

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

B. Anticipation

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

21. I understand that anticipation by inherent disclosure is appropriate only when a prior art reference necessarily includes or discloses the unstated claim element. I also understand that the discovery of a new or previously unreported or

unappreciated property of a prior art composition, or of a scientific explanation for how a prior art composition operates, does not make the prior art composition patentably new to the entity or person that discovered the new property or mode of operation. I further understand that there is no requirement that a POSITA would have recognized the inherent disclosure at the time of the invention.

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

A) The quantity of experimentation necessary;

B) The amount of direction or guidance presented;

C) The presence or absence of working examples;

D) The nature of the claimed invention;

E) The state of the prior art;

F) The relative skill of those in the art;

G) The predictability or unpredictability of the art; and

H) The breadth of the claims.

C. Obviousness

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

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

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

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.

D. Patent Eligible Subject Matter

29. I understand that a patent may be obtained for inventions of any new and useful process, machine, manufacture, or composition of matter, or any new or useful improvement to a process, machine, manufacture, or composition of matter.

30. I understand that patent claims that are directed to abstract ideas are not eligible for patenting. I understand that determining whether a claim recites patent eligible subject matter is a question of law.

E. Specification Requirements

31. I understand that a patent claim is invalid if the specification fails to meet the written description requirement. I understand that for a claim to be supported by a sufficient written description, the original disclosure in the application must reasonably convey to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.

32. I understand that to satisfy the written description requirement, the specification must describe every claim limitation such that a person of ordinary skill, reading the specification, would inherently, necessarily, or immediately envisage the claimed invention.

33. I further understand that while no particular form of disclosure is required or that the specification recite the claimed invention in the exact same words, a description that merely renders the claimed invention obvious does not satisfy the written description requirement. In other words, it not sufficient for purposes of the written description requirement that the disclosure, when combined

with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose.

34. Further, I understand that mere textual support for each individual claim limitations without a description of the specifically claimed combination or actual functioning of the invention that the individual claim limitations together define is not a sufficient disclosure to meet the written description requirement.

35. I understand that dependent claims are supposed to further limit the scope of the independent claims, and if they do not, they are invalid.

F. Indefiniteness

36. I understand that that a claim is indefinite if the claim, when read in light of the specification and the prosecution history, fails to inform those skilled in the art about the scope of the invention with reasonable certainty. I have further been informed that when a claim term can refer to various different methods for determining a measurement or threshold, such term is indefinite if those methods are calculated in different ways that may yield materially different results when the claims, the specification, and the prosecution history do not indicate which method the claims cover.

G. Enablement Requirement

37. It is my understanding that a claimed invention is enabled if the specification does not contain a sufficiently full and clear description of how to make

and use the full scope of the claimed invention. To be enabled, the patent must permit one of skill in the art to make and use the full scope of the claimed invention at the time of original filing without having to conduct undue experimentation. In deciding whether a person having skill in the art would have to experiment unduly in order to make and use of the invention, I understand several factors, known as the *Wands* factors, may be considered: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. I understand that no one or more of these factors alone is dispositive. Rather, whether the degree of experimentation required is undue requires weighing these factors in the context of the claimed invention and the state of the art at the time of the original application.

VI. LEVEL OF ORDINARY SKILL

38. A person having ordinary skill in the art ("POSITA") would have had, as of 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

39. The ’204 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.

40. Plasmapheresis, also known as plasma exchange or therapeutic plasma exchange, has been a clinical procedure since the 1960s. EX1009, 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.

41. 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.

42. 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. EX1009, Chapter 4: Current Instrumentation of Apheresis.

43. 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. EX1007. 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. EX1007.

44. At the time the ’204 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. EX1009, 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. EX1009, 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 cycles[1], 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 ’204 patent. *See, e.g.*, EX1010.

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[1] *See* EX1009, 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.*, EX1009, p. 14, “The pump flow rates—and, thereby, the component collection—are controlled by the microprocessor in response to the optical monitor.”

VIII. ’204 PATENT OVERVIEW

A. The ’204 Patent Relates To Plasma Apheresis

45. The ’204 patent relates to a “system … for collecting plasma” in blood apheresis systems. EX1001, Title, 1:39-41. “Apheresis is a procedure in which individual blood components,” *e.g.*, plasma and red and white blood cells, “can be separated and collected from whole blood.” EX1001, 1:45-47. The ’204 patent relates to plasma apheresis, which is plasma collection. Figure 3 shows one embodiment of a plasma apheresis system.

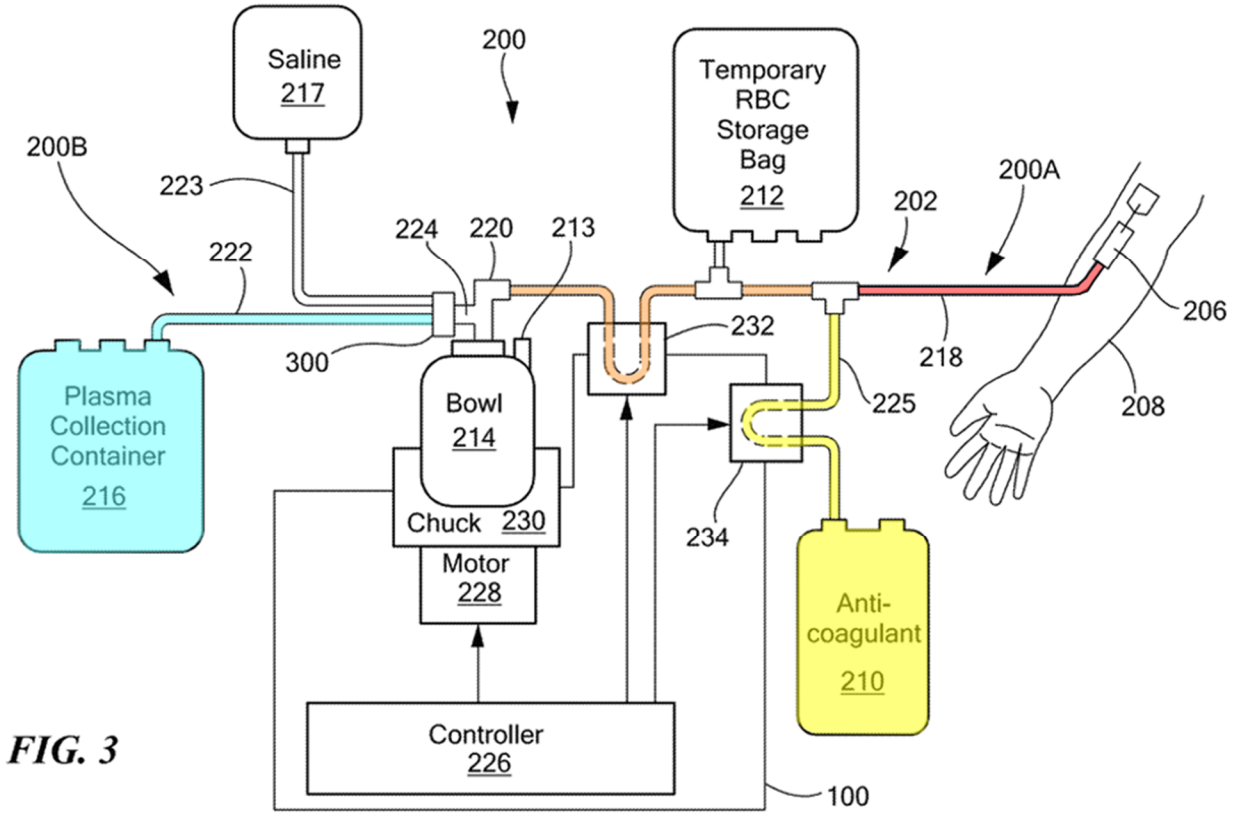


FIG. 3

EX1001, Fig. 3 (annotated).

46. Plasma apheresis involves withdrawing whole blood from a donor's arm using venous access device 206. EX1001, 7:60-63. 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, 8:36-37, 9:24-29. Anticoagulant is introduced in fixed proportions to the whole blood drawn from the donor to prevent blood clotting in the draw line. See EX1010. "[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, 10:54-58.

47. 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, 7:63-65, 8:3-6, 9:54-56. The donor's plasma, i.e., pure plasma, along with anticoagulant introduced during collection, exits the separation device and is collected and stored in a collection container (e.g., a bag, shown in blue above). EX1001, 8:31-35. The anticoagulant and pure plasma combination is called anticoagulated plasma or plasma product. EX1001, 17:4-8, 17:34-36.

48. The FDA established guidelines regarding how much plasma any individual donor is able to donate. See EX1007 These guidelines consider donor parameters, like weight, hematocrit, and sex. *See* EX1007.

B. Purported Invention of the ’204 Patent

49. The ’204 patent purports to solve problems associated with “determin[ing] the total volume of plasma that has been collected” after a donor’s withdrawn whole blood is mixed with anticoagulant by considering a donor’s hematocrit level and the amount of anticoagulant added into the system. EX1001, 2:4-10, 2:20-23, 7:19-24. The ’204 patent discusses three main volumes—target plasma collection volume, anticoagulant volume, and the total collected plasma volume.

50. With respect to target plasma collection volume, the technician can calculate the target plasma collection volume “based, at least in part on the weight of the donor.” EX1001, 3:9-10.

51. Additionally, or alternatively, the technician or system may calculate a donor-specific target pure plasma volume using the donor’s total blood volume. EX1001, 13:41-44. Lemmens’ formula is used to estimate a donor’s total blood volume (TBV) based on their body mass index (BMI). Lemmens’ indexed blood volume (InBV) calculates mL of blood per kilogram using the equation:

$$lnBV = \frac{70}{\sqrt{\frac{BMIp}{22}}}$$

where 70 (mL/kg) is the assumed blood volume for an individual at ideal body weight (BMI = 22 kg/m²). EX1001, 13:60-65. InBV is multiplied by the donor's body weight in kg to calculate TBV in mL. The donor's plasma volume is then determined from the TBV and the donor's hematocrit. EX1001, 13:65-14:2. The system or technician multiplies this plasma volume by a target percentage—typically between 26.5% and 29.5%—to calculate the target pure plasma collection volume. EX1001, 14:3-20. However, the '204 patent also discloses that "the target percentage may be below 26.5% or above 30%," "input directly into the system," or "may be preset from a factory." EX1001, 14:14-20.

52. A technician begins collecting plasma after calculating the target plasma volume. EX1001, 14:21-24. Once the procedure starts, a technician can use an equation to calculate the volume of anticoagulant in a plasma collection bag ("anticoagulant volume"). Specifically, a technician can 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 collection bag. EX1001, 11:20-40. Donors have different hematocrit levels,

which affects the amount of plasma in the donor's whole blood and the anticoagulant volume. EX1001, 10:66-11:12.

53. In the below equation, "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, 11:20-57. Anticoagulated whole blood is extracted blood mixed with anticoagulant.

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

54. Alternatively, the technician can determine, without considering a donor's hematocrit, the amount of anticoagulant added to the system using a "predetermined ratio of anticoagulant per unit anticoagulated whole blood," by monitoring "the number of rotations of the anticoagulant pump"[3] introducing

[3] Because red blood cells' osmolarity prevents anticoagulant from mixing with them, essentially all of the anticoagulant exits bowl 214 and is collected within plasma collection container 216. EX1001, 11:30-34. Thus, subtracting the anticoagulant volume added to the system from the total volume in the collection container estimates the pure plasma volume in the collection container. EX1001, 11:30-34, 11:62-67, 12:33-51.

anticoagulant into this system, "and/or based on the change in weight of the anticoagulant container 210." EX1001, 11:48-57.

55. The '204 patent discloses that the controller uses a weight sensor to monitor the collection container's weight and uses weight to determine the total volume of liquid in the collection container. EX1001, 10:26-28, 10:61-65, 12:33-51. The controller uses this total volume to calculate the anticoagulant and pure plasma volumes in the collection container. EX1001, 11:12-12:51. The '204 patent first calculates the anticoagulant volume. EX1001, 11:58-62. It then calculates the pure plasma volume by subtracting the anticoagulant volume from the total volume of liquid in the collection container. EX1001, 11:45-12:8.

56. The '204 patent repeats any of the above methods to determine the pure plasma volume "until a target volume of pure plasma is collected in the plasma collection container," *e.g.*, the volume set by FDA regulation. EX1001, 11:67-12:8. When a target volume of pure plasma is collected, 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, 12:9-19.

IX. PRIOR ART OVERVIEW

A. Fletcher-Haynes

57. 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. EX1005, 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." EX1005, 48:29-31; 52:13. For example, Fletcher-Haynes' prediction algorithms include a donor's gender, height, weight, hematocrit, and platelet pre-count parameters. EX1005, 27:30-34; 49:19-52:36.

58. Figure 7B illustrates Fletcher-Haynes' collection assembly 10" for separating blood into components. EX1005, 45:58-46:15. Donor's blood is pumped through donor access line 62 (purple) and into inlet line 66 (red), and anticoagulant is pumped from AC container 30 (yellow) into to the inlet line 66. EX1005, 45:22-37, 45:58-63. Blood component separation device 18 separates anticoagulated whole blood into separate components flowing into platelet collect bags 38 and plasma collect bag 54. EX1005,45:63-46:7. The remaining, uncollected blood is pumped back to the donor using return line 70 and the donor line 62. EX1005, 46:10-15.

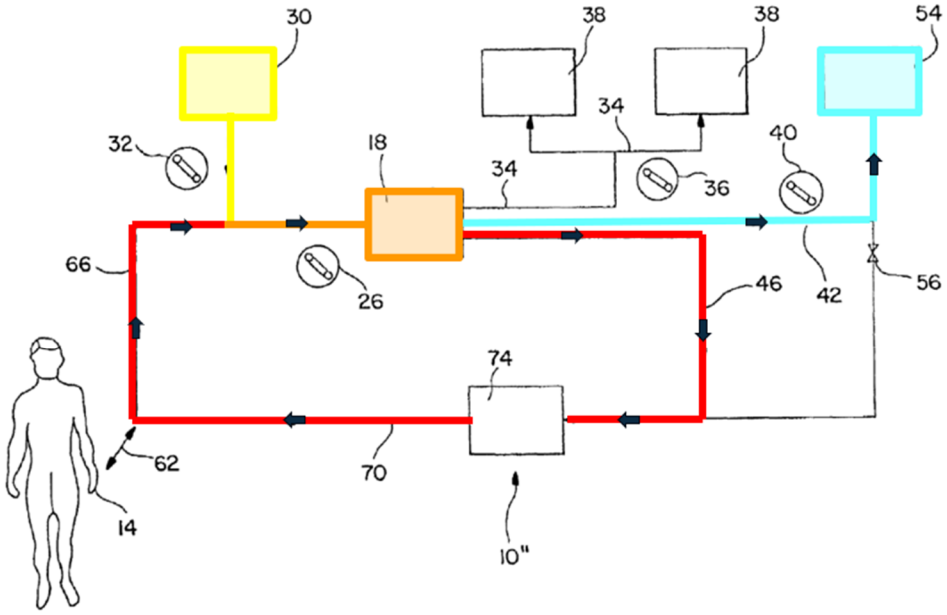


Figure 7B

EX1005, Fig. 7B (annotated).

59. Assembly 10" operates according to a collection procedure derived from procedure goal(s) and may include maximizing "at least one process control parameter." EX1005, 7:38-43, 9:35-44. This maximization is determined by inputting donor-provided data, like height, weight, and blood processing machine type in optimization and prediction models. EX1005, 49:7-18.

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." EX1005, 49:22-26. When executed during a blood separation procedure, the prediction model determines any of parameters (1)-(11) in real-time. EX1005, 34:8-24, 48:66-49:26.

61. Fletcher-Haynes' prediction algorithms may be integrated with its optimization algorithms. Fletcher-Haynes discloses 22 equations that can be incorporated into a prediction model to predict a particular blood component's optimal yield. EX1005, 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, and another is an equation for calculating source plasma volume or a target pure plasma volume collected or to collect. EX1005, 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; and Equation 22 defines the predicted total volume in the source plasma bag (V_{SPB}). EX1005, 49:40-52:17. These equations can be integrated with Fletcher-Haynes' optimization algorithms. EX1005, 58:63-67.

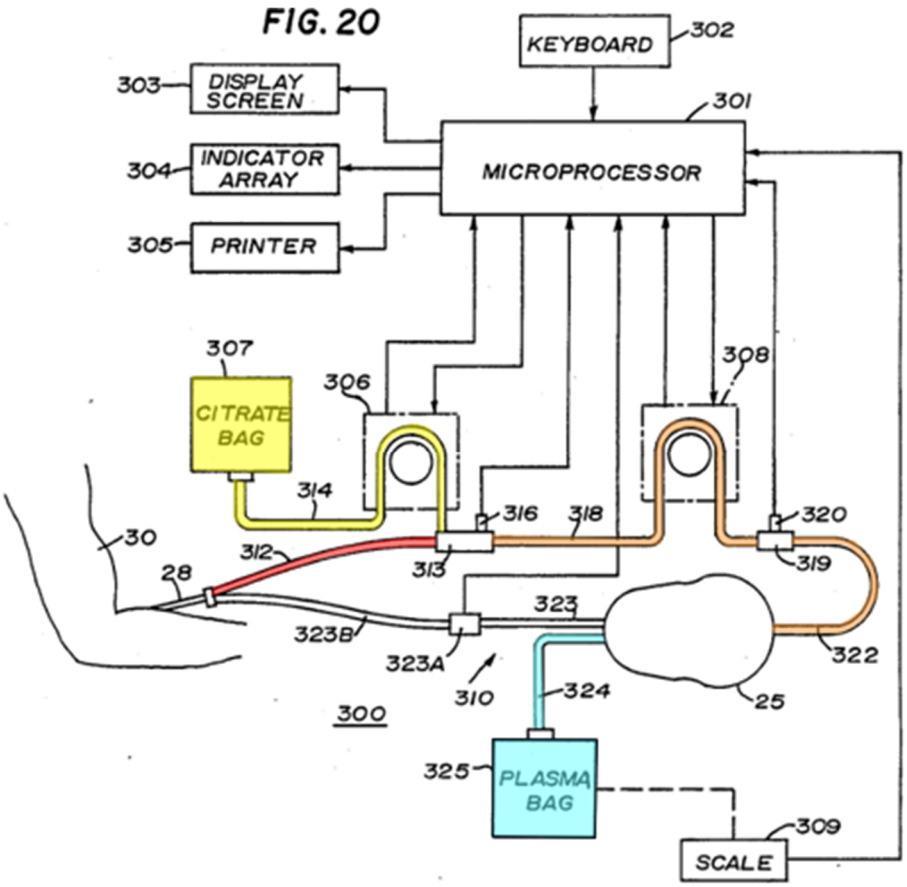
62. Fletcher-Haynes explains that it is preferable during procedures "to have computer/database system 140 exert control over apheresis machine functions, including process control manipulation and optimization." EX1005, 34:8-24, 49:40-52:17. Because computer/database system 140 can control apheresis 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 during those procedures. EX1005, 34:8-24, 49:40-52:17.

B. Lavender

63. 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 in a collected plasma component during a plasma collection procedure, for example to "accurately, safely and economically collect[ ] plasma from a source of blood." EX1004, 3:26-28.

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



EX1004, Fig. 20 (annotated).

65. 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 (a blood anticoagulant) pumped from citrate bag 307. EX1004, 16:57-17:2, 16:45-47. System 300 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.

66. 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 take into account the weight of the collected plasma and anticoagulant solution during the collection process. These calculations are ultimately used to calculate the volume of pure plasma and anticoagulant in the plasma collection bag in real time. EX1004, 20:55-68.

67. 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. Because Lavender's system determines the relationship (or ratio) between the pure plasma volume and the anticoagulant volume in the collection container, a POSITA would readily understand how to convert between the two volumes. By utilizing this relationship, Lavender's determination of the pure plasma volume is based, at least in part, on the volume of anticoagulant.

68. 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 ($MAXPF$), which is determined using a donor's weight. EX1004, cols. 43-44, claim 33.

C. Neyrinck

69. Neyrinck emphasizes the importance of accurately determining total blood volume (TBV) in apheresis procedures to ensure safety and efficacy. EX1006, 38-39. Because physiological variables impact TBV, Neyrinck discloses multiple methods for calculating TBV using height, weight, sex, age, morphology, and BMI. EX1006, pp.38-39. For example, Nadler's formula, widely used in apheresis machines, calculates TBV based on a person's gender, height, weight, and age. EX1006, p.39. Neyrinck's approaches include models for pediatric patients, based on gender and body type, and using body mass index (BMI) (calculated using weight and height) as the primary variable. EX1006, pp.39-40. These methods assign a blood volume per kilogram of body weight depending on the BMI category. EX1006, 40.

X. DETAILED IDENTIFICATION HOW ALL CLAIMS OF THE '204 PATENT ARE UNPATENTABLE

70. The sections below, explain my reasoning why all claims of the '204 patent are unpatentable.

A. Ground I: Fletcher-Haynes anticipates claims 8, 11-15, 17-20, 23-24, and 27-29.

1. Claim 8

i. [8 pre] A system for collecting plasma comprising:

71. To the extent the preamble is limiting, Fletcher-Haynes discloses a system for collecting plasma. Fletcher-Haynes discloses "an extracorporeal blood processing system[]" which utilizes "a method for **collecting** at least one predetermined blood component ("e.g., a collection of platelets or red blood cells or **plasma"**) from a source of whole blood **using a blood component collection system**." EX1005, 1:10-11, 7:33-38.

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

72. Fletcher-Haynes discloses a "single needle assembly… [that] integrates the donor 14 within the blood component separation assembly 10"." EX1005, 45:58-62. "[B]lood is either being removed from or provided back to the donor 14" using "a needle assembly or other blood access device," *e.g.*, a venous access device. EX1005, 1:27-31, 46:12-13. Figs. 7B.

iii. 8[b] a blood component separation device for separating the drawn whole blood into a plasma component and at least 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;

73. Fletcher-Haynes discloses a blood separator (*e.g.*, a blood component collection device 18) which is configured to "separate[] the whole blood … into three primary constituents" including a plasma product (*e.g.*, "plasma product volume plus anticoagulant volume") and a second blood component comprising red blood cells (*e.g.*, "a combination of red and white blood cells"). EX1005, 23:39-41, 45:38-57.

74. Fletcher-Haynes' blood separator contains a plasma output port coupled to a plasma line (*e.g.*, plasma tube 112 that "extend[s] externally of the rotatable device 18"). EX1005, 47:17-34; Figs. 8A & 8B.

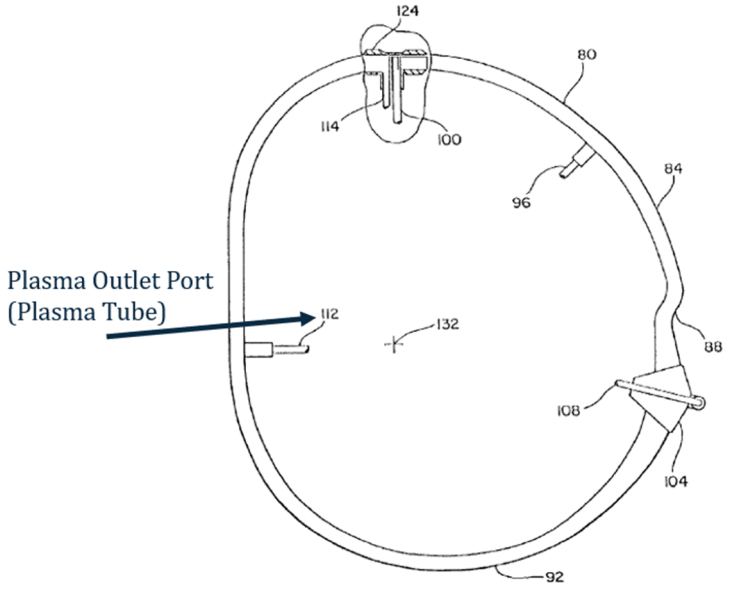
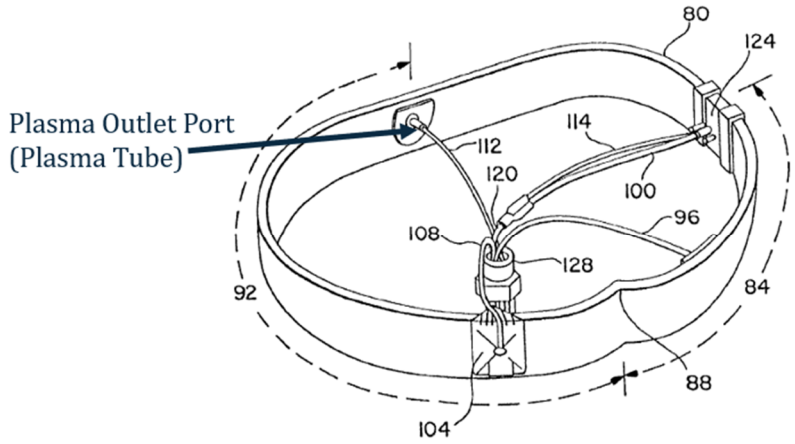


Figure 8B



75. The blood separator is configured to send the separated plasma through the plasma line to the plasma component collection container, as plasma collect bag 54 "is interconnected with the plasma line 42" and plasma tube 112 to "collect the separated plasma." EX1005, 45:51-56, 45:58-62.

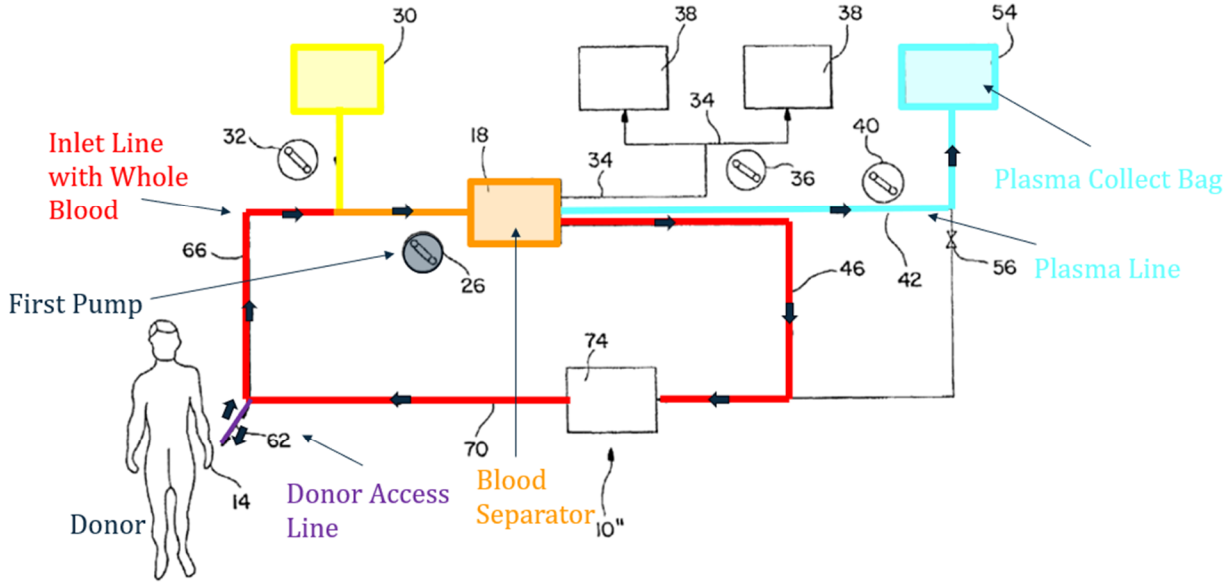


Figure 7B

EX1005, Fig. 7B (annotated).

76. Therefore, Fletcher-Haynes' blood component separation device has a plasma output port coupled to a plasma line configured to send the plasma product to a plasma product collection container.

iv. 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;[4]

77. Fletcher-Haynes discloses a first line (*e.g.*, donor access line 62) connected to the venous access device (*e.g.*, the single needle assembly connected to the donor 14) configured to transport drawn whole blood to the blood component separation device (*e.g.*, blood component collection device 18). EX1005, 45:22-29, 45:63-67. Fletcher-Haynes further discloses that fluid from the blood component separation device 18 (*e.g.*, uncollected blood components) is "provided back to the donor 14" using "the donor access line 62." EX1005, 46:10-15.

4 It is my opinion that the phrase "the flow through the first line being controlled by a first pump" is indefinite because a POSITA would not know how the claimed pump controls the flow through the first line. I offer an interpretation of this limitation solely for the purpose of analyzing the prior art, and not as a concession that the claim language is reasonably clear or definite.

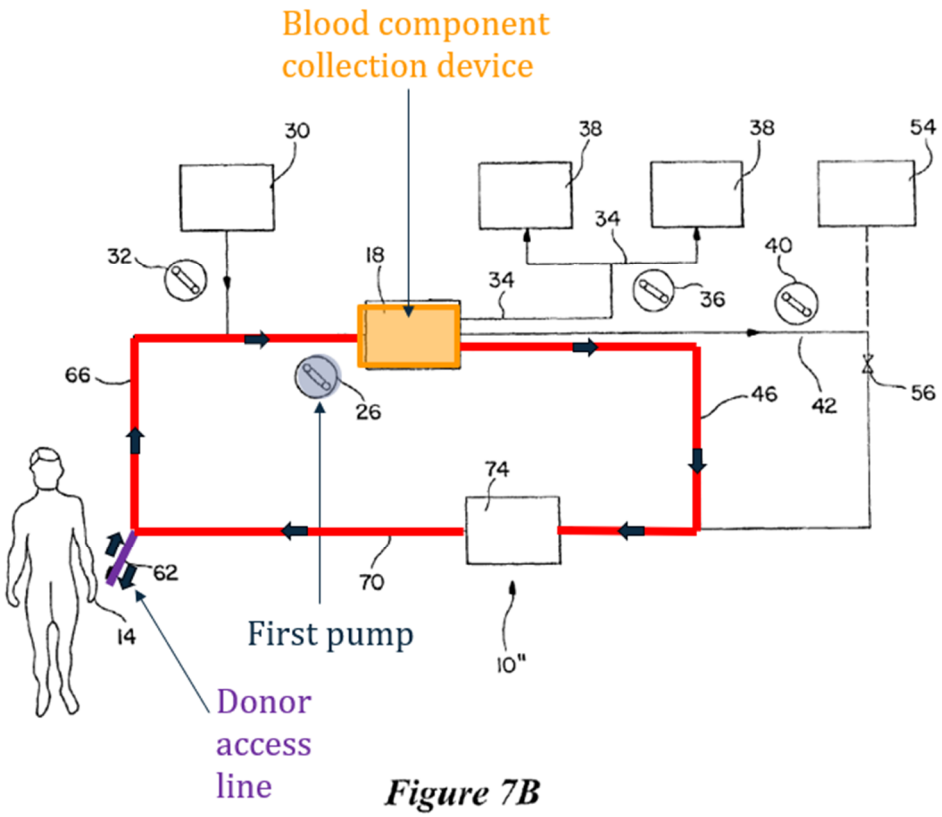


Figure 7B

EX1005, Fig. 7B (annotated).

78. Fletcher-Haynes further discloses "an inlet pump 26 (e.g., a peristaltic pump) to maintain [the] flow" of whole blood from the donor to the blood component separation device through the first line. EX1005, 45:24-29.

v. 8[d] an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

79. As shown in Fig. 7B, Fletcher-Haynes discloses an anticoagulant line (*e.g.*, the line connecting draw line 66 with AC container 30) coupled to an anticoagulant source (*e.g.*, AC container 30). Fletcher-Haynes further discloses that

the anticoagulant line combines anticoagulant with the whole blood, *e.g.*, by providing "anticoagulant from an anticoagulant ('AC') container 30" to the interconnected blood draw line. Whole blood and anticoagulant are combined "[p]rior to the blood of the donor 14 entering the blood component collection device 18." EX1005, 45:29-37. Fletcher-Haynes "utiliz[es] an AC pump 32," *e.g.*, a second pump, "to maintain … flow" of anticoagulant from the anticoagulant source. EX1005, 45:29-37.

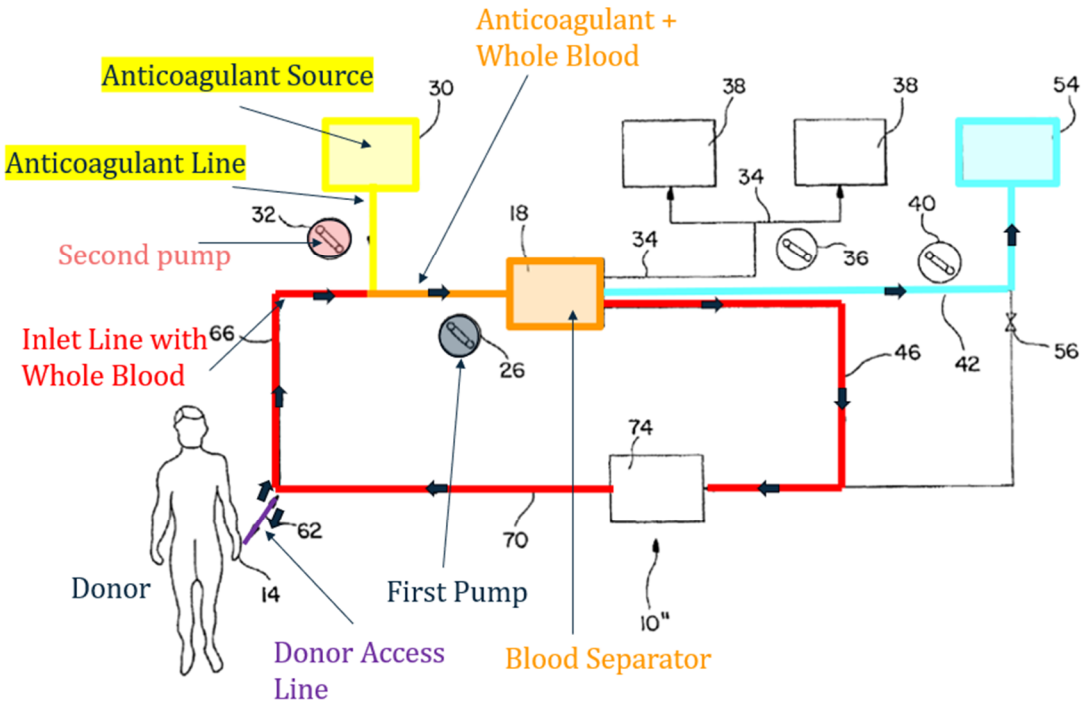


Figure 7B

EX1005, Fig. 7B (annotated).

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

80. Fletcher-Haynes discloses a controller (*e.g.*, the internal control of a blood component collection device) that controls the operation of the blood component separation device (*e.g.*, the blood component collection device 18) and the first pump (*e.g.*, inlet pump 26). EX1005, 53:16-20. 45:24-29. The internal control of a blood component collection device 18 maintains "all actual apheresis control during a procedure" and "perform[s] the collection procedure" by controlling the blood component collection device's hardware. EX1005, 34:12-14, Fig. 9A. For example, the internal control of the blood component separation device controls "the angular velocity of the blood component collection device 18" to "enhance the separation of the various blood components." EX1005, 48:39-48. Moreover, the internal control of a blood collection device 18 maintains control of inlet pump 26, *e.g.*, the first pump, by "maintain[ing] th[e] flow" of whole blood through donor access line 66. EX1005, 45:28.

vii. 8[f] the controller configured to calculate a target plasma amount to collect based, at least in part, on the donor's total blood volume and a hematocrit of the donor,

81. Fletcher-Haynes' controller calculates both a target volume for plasma product (*e.g.*, V_{SPB}, total volume in source plasma bag), which comprises raw plasma

and anticoagulant, and a target volume for pure plasma (*e.g.*, V_{SP}, volume of pure plasma in the source plasma bag), based at least in part on the donor's total blood volume and hematocrit. Fletcher-Haynes' controller runs a "prediction model for predicting a yield of a particular blood component to be collected before a collection procedure is initiated using a compilation of algorithms" which calculates a target volume for plasma product and/or pure plasma. EX1005, 48:1-3.

82. ***First***, Fletcher-Haynes calculates a low, medium, or high AC Ratio (R) using the donor's hematocrit (H) in Equation 9.

$$R = 1 + \frac{2.51}{H} \text{ (low), or}$$

$$\text{R} = 1.33\left(1 + \frac{2.51}{H}\right) \text{ (medium), or}$$

$$\text{R} = 1.67\left(1 + \frac{2.51}{H}\right) \text{ (high)}$$

83. Fletcher-Haynes then determines the fraction of AC in the collected plasma component f_{ACP} using the AC ratio and hematocrit in equation 15.

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

84. ***Second***, Fletcher-Haynes calculates total blood volume using a donor's weight (W), height (L), and gender in equation 10.

$$V_B = 604 + 0.006012L^3 + 14.6W \text{ ml (male)}$$

$$= 183 + 0.005835L^3 + 15.0W \text{ ml (female)}$$

85. ***Third***, in equation 17, Fletcher-Haynes calculates a target volume of pure plasma (V_{SP}) using the total blood volume.

$$\begin{cases} V_{SP} = 0 \\ = V_{CON} - V_C \\ = f_{SP}V_B - V_C \\ = \text{specified as modified input} \end{cases} \geq 0$$

86. ***Finally***, Fletcher-Haynes calculates a volume of plasma product (V_{SPB}) in equation 22.

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

Expanding Equation 22 reveals that V_{SPB} is a sum of volume of pure plasma (V_{SP}) and volume of added anticoagulant ($V_{SP} * f_{ACP}$).

87. These values are target values because Fletcher-Haynes can run the prediction model "before the collection procedure is actually initiated." EX1005, 53:36-38. Therefore, Fletcher-Haynes calculates a target volume for plasma product using a donor's blood volume and hematocrit.

viii. 8[g] the donor's total blood volume based, at least in part, on a weight and height of the donor,

88. The internal control of Fletcher-Haynes' blood component separation device calculates the "total blood volume of the donor or patient in mL," V_B, in equation 10:

$$V_B = 604 + 0.006012L^3 + 14.6W \text{ ml (male)}$$

$$= 183 + 0.005835L^3 + 15.0W \text{ ml (female))}$$

using the height (L) and weight (W) of the donor. EX1005, Eq. 10, 47:61-48:3, 51:61, 52:6, 52:15.

ix. 8[h] the target plasma amount to collect tailored to the donor.

89. Fletcher-Haynes discloses a method and system that collects plasma that solves the problem of having "a multitude of collection choices [and] a multitude of donors with differing physiologies, each being subject to potential variations in collection procedures." EX1005, 2:15-19. As such, Fletcher-Haynes "better satisf[ies] the individual needs of patients" by calculating a target plasma amount to collect (*e.g.*, V_{SP} or V_{SPB}) that is tailored to the individual's characteristics such as height, weight, gender, and hematocrit. EX1005, 2:43.

2. Claim 11

i. The system according to claim 8, wherein the controller is further configured to calculate the donor's total blood volume.

90. *See* §X.A.1.vii (limitation 8[g]).

3. Claim 12

i. The system according to claim 8, wherein the calculated target plasma amount to collect is an optimized safe amount to be collected from the donor.

91. Fletcher-Haynes calculates a target plasma collection amount that is an optimized safe amount. Fletcher-Haynes' optimization model "integrally incorporate[s] the prediction model" such that the prediction model "may be used for both product-based and time-based optimizations." EX1005, 58:61-67. The product-based optimization process outputs "optimal values" of target volumes of pure plasma (*e.g.*, V_{SP}) and anticoagulated plasma (*e.g.*, V_{SPB}). EX1005, 1:35-47.

92. Fletcher-Haynes' optimized target collection amounts are safe amounts that "satisfy the individual needs of patients." EX1005, 2:43. For example, prior to starting a donation procedure, a technician cannot select a donation procedure "which are not available due to physical (and/or safety) constraints such as the donor not meeting a minimum hematocrit or total blood volume preferred therefor." EX1005, 29:41-43.

4. Claim 13

i. The system according to claim 8, wherein the controller is further configured to: return, after collecting at least a portion of the target plasma amount to collect, the contents of the blood component separation device to the donor through the first line.

93. Fletcher-Haynes discloses a blood collection system "wherein blood is removed from a donor, processed in" a centrifuge, "and the uncollected components" from the centrifuge are "thereafter returned to the donor." EX1005, 1:32-36. "[A]ll actual apheresis control during a procedure," *e.g.*, when to draw and return blood "remains resident in the apheresis machine 10 itself" *e.g.*, the "internal control of a blood collection device 18." EX1005, 34:12-14, 52:40-43. Therefore, Fletcher-Haynes' system contains a controller that returns uncollected blood components after collecting at least a portion of the target plasma collection volume.

94. The uncollected blood components are returned to the donor through the first line because in a single-needle configuration, "only a single line is connected to the donor 14, namely the donor access line." EX1005, 46:10-15.

5. Claim 14

i. The system according to claim 8, wherein the target plasma amount to collect is a target amount of pure plasma to collect or a target amount of anticoagulated plasma to collect.

95. Fletcher-Haynes' prediction algorithm calculates a target plasma amount to collect, V_{SP}, that is a target "volume of pure plasma" to collect "in [the] source plasma bag" in equation 17:

$$\begin{cases} V_{SP} = 0 \\ = V_{CON} - V_C \\ = f_{SP}V_B - V_C \\ = \text{specified as modified input} \end{cases} \geq 0$$

EX1005, Eq. 17, 52:13.

96. Fletcher-Haynes' prediction algorithm also calculates a target plasma amount to collect that is a target amount of anticoagulated plasma to collect, *e.g.*, V_{SPB}, "total volume in [the] source plasma bag," in equation 22: $V_{SPB} = V_{SP}(1 + f_{ACP})$. EX1005, Eq. 22, 52:14.

6. Claim 15

i. 15[preamble] A method for collecting plasma comprising:

97. To the extent the preamble is limiting, Fletcher-Haynes discloses "an extracorporeal blood processing system[]" which utilizes "a method for **collecting** at least one predetermined blood component ("e.g., a collection of platelets or red

blood cells or **plasma"**) from a source of whole blood **using a blood component collection system**." EX1005, 1:10-11, 7:33-38.

ii. 15[a] determining individual characteristics of a donor, the individual characteristics of the donor including a weight, a height and a hematocrit of the donor;

98. Fletcher-Haynes determines, *e.g.*, by having an apheresis system receive an input of donor characteristics on a touchscreen, individual characteristics of a donor which include "height, weight, gender, and platelet pre-count or hematocrit" via the touchscreen. EX1005, 1:48-52.

iii. 15[b] calculating a donor total blood volume based, at least in part, on the weight and height of the donor;

99. *See* §§X.A.1.viii, X.A.2.i (limitation 8[g], claim 11).

iv. 15[c] calculating a target plasma amount to collect based, at least in part, on the calculated donor total blood volume and the hematocrit of the donor,

100. *See* §§X.A.1.vii (limitation 8[f]).

v. 15[d] the target plasma amount to collect being tailored to the individual characteristics of the donor;

101. *See* §§X.A.1.ix (limitation 8[h]).

vi. 15[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;

102. Fletcher-Haynes withdraws whole blood from donor 14 using "a single needle assembly," *e.g.*, a venous access device. EX1005, 45:58-63. "Whole blood

… initially flows through a donor access line 62," *e.g.*, a first line, "which is fluidly connected with the blood component collection device 18," *e.g.*, the blood component separation device. EX1005, 45:63-67.

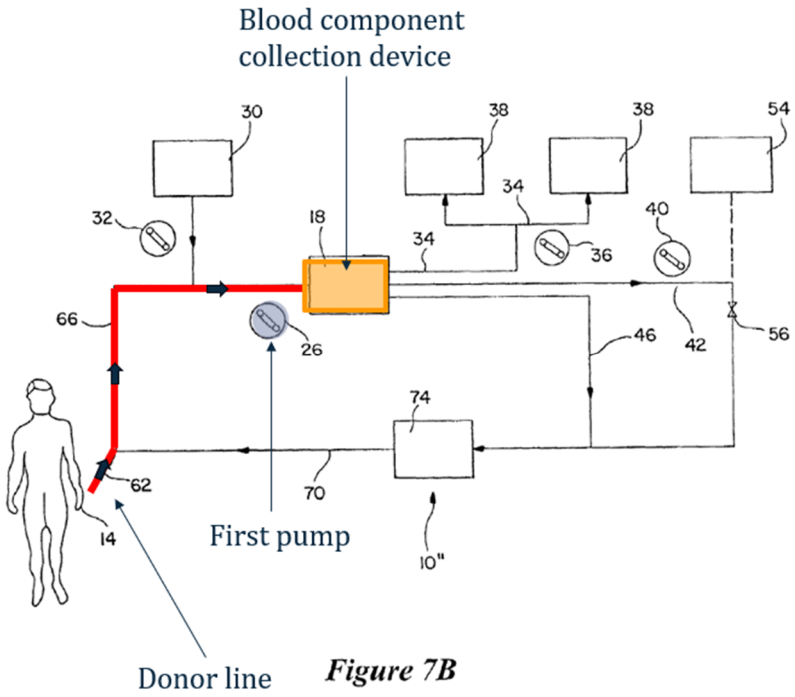


Figure 7B

EX1005, Fig. 7B (annotated).

vii. 15[f] introducing anticoagulant into the withdrawn whole blood through an anticoagulant line;

103. Fletcher-Haynes introduces anticoagulant to the withdrawn whole blood using an anticoagulant line connected to an anticoagulant source. *See* §X.A.1.v (limitation 8[d]).

viii. 15[g] separating the withdrawn whole blood into a plasma component and at least a second blood component; and

104. Fletcher-Haynes discloses a blood separator (*e.g.*, a blood component collection device 18) which is configured to "separate[] the whole blood … into three primary constituents" including a plasma product (*e.g.*, "plasma product volume plus anticoagulant volume") and a second blood component comprising red blood cells (*e.g.*, "a combination of red and white blood cells"). EX1005, 23:39-41, 45:38-57; *see also* §X.A.1.iii (limitation 8[b]).

ix. 15[h] collecting the plasma component from the blood component separation device and into a plasma collection container.

105. Fletcher-Haynes "collect[s] the separated plasma" *e.g.*, the plasma component, "in … a plasma collect bag," *e.g.*, the plasma collection container. EX1005, 45:51-55. The plasma collect bag 54 receives plasma from a "plasma line 42" that is connected to the output of the blood component collection device 18. EX1005, 45:51-55, 47:29-34, Fig. 7B.

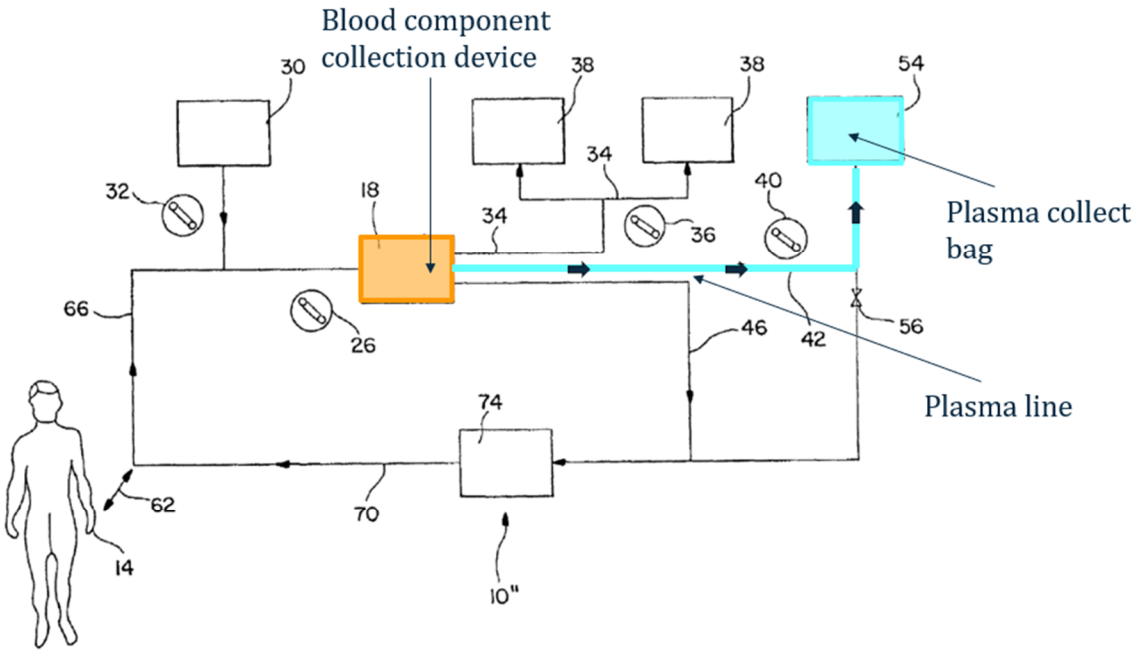


Figure 7B

EX1005, Fig. 7B (annotated).

7. Claim 17

i. The method according to claim 15, further comprising: returning, after collecting at least a portion of the target plasma amount to collect, the contents of the blood component separation device to the donor through the first line.

106. *See* §X.A.4.i (claim 13).

8. Claim 18

i. The method according to claim 15, wherein the target plasma amount to collect is a target amount of pure plasma to collect.

107. Fletcher-Haynes calculates a target volume of pure plasma to collect, V_{SP}. *See* §X.A.5.i (claim 14).

9. Claim 19

i. The method according to claim 15, wherein the target plasma amount to collect is a target amount of anticoagulated plasma to collect.

108. Fletcher-Haynes calculates a target volume of anticoagulated plasma to collect, V_{SPB}. *See* §X.A.5.i (claim 14).

10. Claim 20

i. The method according to claim 15, wherein the target plasma amount to collect is an optimized safe amount to be collected from the donor.

109. *See* §X.A.3.i (claim 12).

11. Claim 23

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

110. *See* §X.A.1.i (limitation 8[pre]).

ii. 23[a] a venous-access device for drawing whole blood from a donor and returning blood components to the donor;

111. *See* §X.A.1.ii (limitation 8[a]).

iii. 23[b] a blood component separation device for separating the drawn whole blood into a plasma component and at least 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;

112. *See* §X.A.1.iii (limitation 8[b]).

iv. 23[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;

113. *See* §X.A.1.iv (limitation 8[c]).

v. 23[d] an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

114. *See* §X.A.1.v (limitation 8[d]).

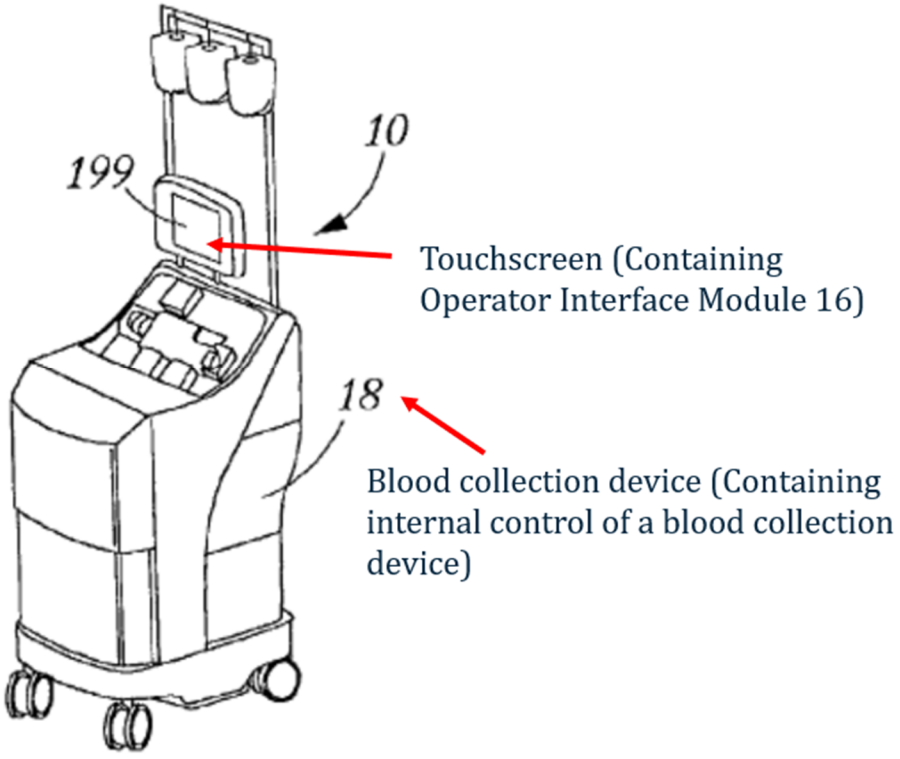
vi. 23[e] a controller configured to control the operation of the blood component separation device and the first pump,

115. *See* §X.A.1.vi (limitation 8[e]).

vii. 23[f] the controller configured to (1) receive individual characteristics of the donor, the individual characteristics including a weight, height, and hematocrit of the donor, and

116. Fletcher-Haynes discloses that "data entry, manipulation and storage may [] be performed at/on each machine using, for example, respective interfaces,

which here are … touchscreen input/output devices." EX1005, 10:12-15; 53:20-25, 52:43-45, Fig. 1A. Fletcher-Haynes receives an input of a donor's individual characteristics, including "height, weight, gender, and platelet pre-count or hematocrit," via the touchscreen. EX1005, 1:48-52. These input values "are downloaded to the internal control of the blood collection device 18," *e.g.*, the controller. EX1005, 54:8-11. The process of downloading the input values "may include encoding of a computer program of instructions for executing [the] computer process," meaning that the controller is configured to receive the donor's weight, height, and hematocrit. EX1005, Fig. 9A, 8:24-34.



EX1005, Fig. 1A (annotated).

viii. 23[g] (2) calculate a target plasma amount to collect based, at least in part, on the donor's total blood volume and a hematocrit of the donor,

117. *See* §§X.A.1.vii, X.A.6.iv (limitation 8[f], 15[c]).

ix. 23[h] the donor's total blood volume based, at least in part, on the weight and height of the donor,

118. *See* §§X.A.1.viii, X.A.6.iii, X.A.2.i (limitations 8[g], 15[b] claim 11).

x. 23[i] the target plasma amount to collect being tailored to the individual characteristics of the donor.

119. *See* §§X.A.1.ix, X.A.6.v (limitation 8[h], 15[d]).

12. Claim 24

i. The system of claim 23, wherein the controller is further configured to calculate the donor's total blood volume.

120. *See* §§X.A.1.vii, X.A.2.i, X.A.6.iii, X.A.12.ix (limitations 8[g], & 15[b], 23[h], claim 11).

13. Claim 27

i. The system according to claim 23, wherein the controller is further configured to: return, after collecting at least a portion of the target plasma amount to collect, the contents of the blood component separation device to the donor through the first line.

121. *See* §§X.A.4.i, X.A.7.i (claims 13, 17).

14. Claim 28

i. The system according to claim 23, wherein the target plasma amount to collect is a target amount of pure plasma to collect or a target amount of anticoagulated plasma to collect.

122. *See* §§X.A.5.i, X.A.8.i, X.A.9.i (claims 14, 18-19).

15. Claim 29

i. The system according to claim 23, wherein the target plasma amount to collect is an optimized safe amount to be collected from the donor.

123. *See* §§X.A.3.i, X.A.12.i (claims 12, 20).

B. Ground II: Fletcher-Haynes in view of Lavender renders obvious claims 1, 3-7, 9, 21-22, 25, and 30.

1. It would have been obvious for a POSITA to combine Fletcher-Haynes and Lavender and would have had a reasonable expectation of success when doing so

124. A POSITA would have been motivated to modify Fletcher-Haynes' system in view of Lavender's disclosures, and would have had a reasonable expectation of success in doing so, because 1) each relates to plasma apheresis, 2) each applies substantially similar techniques to achieve similar results, and 3) the functionality of Fletcher-Haynes' system would not change with the further addition of certain of Lavender's disclosures.

125. Like Fletcher-Haynes, Lavender "relates to the collection of blood, and, in particular, to the fractioning of blood to collect blood substances, such as plasma"

and also uses donor information to improve blood component collection, resulting in "an easier, safer, and more economical method of harvesting plasma." EX1004, 1:11-13, 11:23-26.

126. Further, Fletcher-Haynes tracks "the current collection status" for the "blood product … which may be in the process of being collected as part of a procedure." EX1005, 35:38-41. Fletcher-Haynes repeatedly runs an optimization procedure to determine a target volume of pure and diluted plasma to collect. EX1005, 54:6-12, Eqs. 21-22. Similarly, Lavender calculates a target volume of pure and diluted plasma to collect before beginning its collection operations, which are executed in its Main Loop. EX1004, Table VI, §2. Thus, a POSITA would have turned to Lavender to supply the requisite computer code related to implementing Fletcher-Haynes' procedure tracking. EX1004, cols. 41-44.

127. Additionally, incorporating Lavender's teachings of tracking collection into Fletcher-Haynes' system would have been a routine, minor change to the system that would have yielded predictable results. Lavender's Main Loop contains the same steps as the Fletcher-Haynes procedure. Before beginning a procedure, Lavender and Fletcher-Haynes calculate target volumes of pure plasma. EX1004, Table VI, §2g; EX1005, Eq. 21, 47:60-48:3. During the procedure, Lavender and Fletcher-Haynes monitor the volume of pure plasma collected. EX1004, Table VI,

§5B; EX1005, Fig. 5B, 35:36-41. Lastly, Fletcher-Haynes and Lavender stop the collection procedure at the "plasma volume limit," EX1005, 48:27-34, and the code in Lavender's Main Loop shows that the plasma collection procedure is stopped when the volume of pure plasma equals the target volume of pure plasma. EX1004, Table VI, §5C.

128. Further, 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.

129. 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. A POSITA would understand that in Lavender $R = \frac{(QB+QC)}{QC} = \frac{QB}{QC} + 1$, where QB is blood flow (mL/min) and QC is citrate flow (mL/min), so that $\frac{QB}{QC} = R - 1$. Lavender's equation TABLE VI, 2.a states that $\frac{QP}{QB} = 1 -$ HCTD. Hence a POSITA would understand from Lavender's equation 2.b., which recites $QC = QP * CF$, that CF $=$

$\frac{\mathrm{QC}}{\mathrm{QP}} = \frac{\mathrm{QC}}{\mathrm{QB}} * \frac{\mathrm{QB}}{\mathrm{QP}} = \frac{1}{(\mathrm{R}-1)} * \frac{1}{(1-\mathrm{HCTD})}$ or $\mathrm{CF} = [(R-1) * (1-HCTD)]^{-1}$, which is the same equation as Fletcher-Haynes f_{ACP}.

130. As a third example, 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 $TDPF = TPF * (1 + CF)$, which is equivalent to Fletcher-Haynes' Eq. 22, which recites $V_{SPB} = V_{SP}(1 + f_{ACP})$.

131. Incorporating Lavender's loop code into Fletcher-Haynes' system would have been a known software modification that would have yielded predictable results. That is, incorporating Lavender's Main Loop into Fletcher-Haynes' apheresis system entails the mere use of similar equations to improve similar systems and methods in the same way.

2. Claim 1

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

132. *See* §X.A.6.i (limitation 15 [preamble]).

ii. 1[a] calculating a donor total blood volume based, at least in part, on a weight and a height of a donor;

133. *See* §§X.A.1.vii, X.A.2.ii, X.A.6.iii, X.A.12.i (limitations 8[g] & 15[b], claims 11 & 24).

iii. 1[b] calculating a target plasma amount to collect based, at least in part, on the calculated donor total blood volume and a hematocrit of the donor,

134. *See* §§X.A.1.vii, X.A.6.iv, X.A.11.viii (limitations 8[f], 15[c], 23[g]).

iv. 1[c] the target plasma amount to collect tailored to the donor;

135. *See* §§X.A.1.ix, X.A.6.v, X.A.11.x (limitations 8[h], 15[d], 23[i]).

v. 1[d] 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 of a blood processing system,

136. Fletcher-Haynes withdraws whole blood from the donor through a venous-access device and a first line, the first line connected to a blood component separation device. *See* §X.A.6.vi (limitation 15[e]). Fletcher-Haynes' blood component separation device 18 is a part of a "blood component collection and information management system" that is "implemented at a blood bank/center." EX1005, 9:48-53.

vi. 1[e] the blood processing system having a controller configured to stop collecting plasma when the target plasma amount to collect has been collected into a plasma collection container;

137. Fletcher-Haynes in view of Lavender renders obvious limitation 1[e].

138. Fletcher-Haynes discloses a controller (*e.g.*, the internal control of a blood component separation device) within a blood component separation device

(*e.g.*, blood component collection device) configured to stop collecting the plasma component when the target plasma amount to collect has been collected into the plasma collection container (*e.g.*, plasma bag 54). EX1005, 48:27-31.

139. Fletcher-Haynes further discloses that the blood component separation device is part of a blood processing system. For example, Fletcher-Haynes discloses a blood processing "system 2 [that] would typically be implemented at a blood bank/center." EX1005, 9:52-53. "The system may include a substantially centralized computing/data storage assembly" and a "separation collection assembly 10 [that] preferably includes a blood component separation and collection device as an integral part thereof." EX1005, 9:53-55, 9:63-66, Fig. 1A.

140. Lavender discloses that the controller is configured to stop collecting plasma when the target plasma amount to collect has been collected into a plasma collection container. Lavender runs a main loop that continues to collect plasma until a target volume of raw plasma is collected, *e.g.*, until $TPF = MAXPF$, at which point, Lavender's controller "stops the pumps." EX1004, Table VI, §5C, 20:62-68; 21:61-22:2.

141. As I discuss in §X.B.1, it would have been obvious to incorporate Lavender's main loop into Fletcher-Haynes' plasma collection system, and a POSITA would have had a reasonable expectation of success in doing so. Therefore,

Fletcher-Haynes in view of Lavender the blood processing system having a controller configured to stop collecting plasma when the target plasma amount to collect has been collected into a plasma collection container.

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

142. *See* §X.A.1.v, X.A.6.vii, X.A.11.v (limitations 8[d], limitation 15[f], 23[d]).

viii. 1[g] separating the withdrawn whole blood into a plasma component and at least a second blood component; and

143. *See* §§X.A.1.iii, X.A.6.viii, X.A.11.iii (limitations 8[b], 15[g], 23[b]).

ix. 1[h] collecting the plasma component from the blood component separation device into the plasma collection container until the target plasma amount to collect is reached in the plasma collection container.

144. As I discuss in §X.A.6.ix (limitation 15[h]), Fletcher-Haynes collects the plasma component from the blood component separation device into the plasma collection container. As I discuss in §X.B.2.vi (limitation 1[e]), it would have been obvious for a POSITA to incorporate Lavender's Main Loop into Fletcher-Haynes' system such that the controller would continue collecting plasma until the target plasma amount to collect is reached in the plasma collection container.

3. Claim 3

i. The method according to claim 1, wherein the calculated target plasma amount to collect is an optimized safe amount to be collected from the donor.

145. *See* §§X.A.3.i, X.A.12.i, X.A.15.i (claims 12, 20, 29).

4. Claim 4

i. The method according to claim 1, further comprising: returning, after collecting at least a portion of the target plasma amount to collect, the contents of the blood component separation device to the donor through the first line.

146. *See* §§X.A.4.i, X.A.7.i, X.A.13.i (claims 13, 17, 27).

5. Claim 5

i. The method according to claim 1, wherein the target plasma amount to collect is a target amount of pure plasma to collect.

147. *See* §§X.A.5.i, X.A.8.i, X.A.14.i (claims 14, 18, 28).

6. Claim 6

i. The method according to claim 1, wherein the target plasma amount to collect is a target amount of anticoagulated plasma to collect.

148. *See* §§X.A.5.i, X.A.9.i, X.A.14.i (claim 14, 19, 28).

7. Claim 7

i. The method according to claim 1, further comprising: monitoring an amount of plasma component collected within the plasma collection container.

149. Fletcher-Haynes performs "real time monitoring of procedures … to know the status of [the] collection" of plasma. EX1005, 34:25-28. For example, Fletcher-Haynes' collection tracking "preferably shows the … current collection status for each of the three blood product types (platelets, plasma, and RBC) which may be in the process of being collected as part of a procedure." EX1005, 35:36-41.

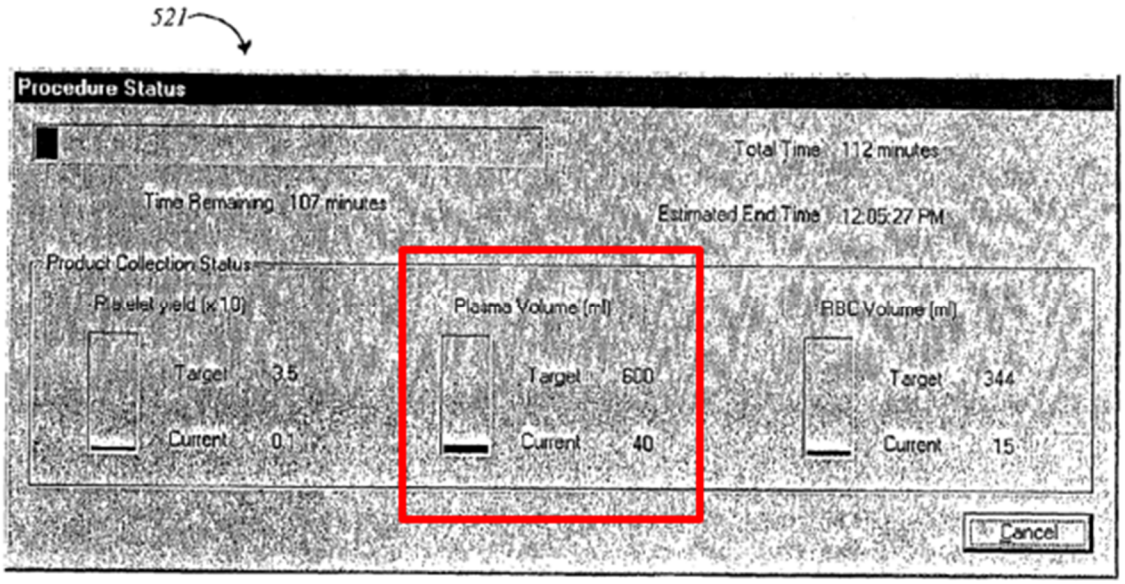


Figure 5B

EX1005, Fig. 5B. The amount of plasma component collected shown in Fig. 5B in Fletcher-Haynes is the amount of plasma component collected within the plasma collection container because Fletcher-Haynes collects plasma in a plasma collect bag, *e.g.*, "plasma collect bag 54." EX1005, 45:51-55.

8. Claim 9

i. The system according to claim 8, wherein the controller is further configured to stop collecting plasma when the target amount of plasma to collect has been collected into the plasma collection container.

150. Lavender discloses a controller (*e.g.*, microprocessor 301) that "cycles through the main loop" that repeatedly calculates the amount of plasma collected during a plasma donation procedure. EX1004, 16:40-45, 20:62-68. Lavender's microcontroller 301 is coupled to "a blood pump 308" for controlling the blood drawing process. EX1004, Fig. 20, 16:45-50. Lavender collects plasma until a target volume of raw plasma is collected, *e.g.*, until $TPF = MAXPF$. EX1004, Table VI, §5C. When "the desired weight of plasma has been collected," Lavender's microcontroller "stops the pumps," thereby stopping plasma collection. EX1004, 21:62-22:6.

9. Claim 21

i. The method according to claim 15, further comprising: stopping the collection of the plasma component from the blood component separation device into the plasma collection container when the target plasma amount to collect is reached in the plasma collection container.

151. *See* §X.B.8.i (claim 9).

10. Claim 22

i. The method according to claim 15, wherein the blood component separation device is part of a blood processing system, the blood processing system having a controller configured to stop collecting the plasma component when the target plasma amount to collect has been collected into the plasma collection container.

152. As I discuss in §X.B.2.vi (limitation 1[e]) and §§X.B.9.i, X.B.10.i (claims 9, 21), Fletcher-Haynes in view of Lavender discloses a blood processing system having a blood component separation device with an internal controller that is configured to stop collecting plasma when the target plasma amount to collect has been collected into a plasma collection container.

11. Claim 25

i. The system according to claim 23, wherein the controller is further configured to stop collecting the plasma component when the target amount of plasma to collect has been collected into the plasma collection container.

153. *See* §X.B.8.i, X.B.9.i (claims 9, 21).

12. Claim 30

i. The system according to claim 23, further comprising: a plasma collection container weight sensor configured to monitor a volume or weight of plasma component collected within the plasma collection container.

154. Lavender discloses "a scale 309 … for weighing the collected plasma," *e.g.*, the plasma collection bag 325, "the scale being coupled to the microprocessor 301 for transmitting weight information thereto." EX1004, 16:50-53. Lavender monitors the weight of the plasma collection container, *e.g.*, the plasma collection bag 325, by "repeatedly performing the [weight] measurements," converting the weight into a volume, and "updating" the measured volume of the plasma collection container "approximately every two seconds." EX1004, 20:62-68.

C. Ground III: Fletcher-Haynes in view of Neyrinck renders obvious claims 10, 16, and 26.

1. It would have been obvious for a POSITA to combine Fletcher-Haynes and Neyrinck

155. A POSITA would have been motivated to modify Fletcher-Haynes' system with the total blood volume (TBV) calculation in Neyrinck and would have had a reasonable expectation of success in doing so because 1) each relates to plasma apheresis, 2) each applies substantially similar techniques to achieve similar results, and 3) the functionality of Fletcher-Haynes' prediction algorithm would not change

after replacing Nadler's formula in Fletcher-Haynes' equation 10 with Neyrinck's formula to calculate total blood volume using BMI.

156. First, Fletcher-Haynes and Neyrinck are analogous pieces of art in plasma apheresis. Fletcher-Haynes discloses an "extracorporeal blood processing system[]" which has "optimization capabilities" to collect the maximum amount of plasma "from donors with differing physiologies." EX1005, 1:10-14, 2:15-19. Neyrinck similarly discloses methods for a donation center "to obtain an optimal [plasma] product" that considers the individual physical characteristics of a donor because "not all donors/patients should be addressed in the same way." EX1006, 38.

157. Second, both Neyrinck and Fletcher-Haynes apply substantially similar techniques of calculating donor-specific blood volumes to achieve optimal plasma collection volumes during an apheresis procedure. Fletcher-Haynes's equation 10 calculates a donor's total blood volume using Nadler's formula and uses this to calculate a customized target plasma collection volume. EX1005, Eq. 10. Neyrinck also discloses using Nadler's formula to calculate a donor's total blood volume. EX1006, 39. Neyrinck further discloses a formula that calculates a donor's total blood volume which "take[s] into account the physics of the person" by considering a donor's BMI and/or whether a donor is "obese, thin, normal, or muscular."

158. A POSITA designing Fletcher-Haynes' prediction algorithm would have been motivated to use a more accurate equation to calculate total blood volume, *e.g.*, because people of the same weight or height may have different body morphologies or ages that influence their total blood volumes. A POSITA would have turned to Neyrinck for its method of calculating total blood volume using BMI, as Neyrinck discloses calculating total blood volume based on the donor's weight, height, sex, age, morphology, and BMI.

159. Third, replacing Nadler's formula with an equation that considers BMI would not change the intended functionality of Fletcher-Haynes' prediction algorithm. Fletcher-Haynes' prediction algorithm using Nadler's formula to calculate total blood volume already uses the same variables (height and weight) used in Neyrinck's method that employs BMI. A POSITA would have had a reasonable expectation of success in adding the functionality as it only requires simple software modifications to Fletcher-Haynes' total blood volume equation. EX1005, Eq. 10, 9:48-63.

2. Claim 10

i. The 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 target plasma amount to collect calculated based, at least in part, on the donor's body mass index.

160. Neyrinck discloses calculations in an apheresis machine (*e.g.*, Fletcher-Haynes' blood component separation device) that "obtain an optimal product without putting [a] donor/patient at risk" by accounting for differences in the "total blood volume (TBV) of the donor/patient." EX1006, 38. Specifically, Neyrinck calculates a total blood volume in relation to body mass index (BMI). First, Neyrinck calculates the BMI of a patient using height (Ht) and weight (Wt) in the following formula: $BMI = \frac{Wt}{Ht^2}$. EX1006, 40. Next, Neyrinck calculates a blood volume per kg of body weight using the BMI in Table III, reproduced below. EX1006, 40.

	BMI < 18.5	BMI 18.5-24.9	BMI 25-29.9	BMI > 30
Blood volume	80 mL/kg	70 mL/kg	65 mL/kg	55 mL/kg

161. Lastly, "[b]ased on the BMI, the bodyweight of the person needs to be multiplied by" the blood volume per kg of bodyweight "to achieve the TBV." EX1006, 39-40.

162. As I discuss in §X.C.1, it would have been obvious to a POSITA to replace Fletcher-Haynes' equation for TBV with the alternative TBV equation disclosed in Neyrinck, and a POSITA would have had a reasonable expectation of success in making the modification. It would have been obvious to a POSITA to then use Neyrinck's calculated TBV as V_B in Fletcher-Haynes' equation 17 to calculate a target volume of pure plasma to collect, *e.g.*, V_{SP}.

$$\begin{cases} V_{SP} = 0 \\ = V_{CON} - V_C \\ = f_{SP}V_B - V_C \\ = \text{specified as modified input} \end{cases} \geq 0$$

163. EX1005, Eq. 17. Therefore, Fletcher-Haynes in view of Neyrinck renders obvious a controller configured to calculate the donor's body mass index based, at least in part on the weight and height of the donor, the target plasma amount to collect calculated based, at least in part, on the donor's body mass index.

3. Claim 16

i. The method according to claim 15, further comprising: calculating the donor's body mass index based, at least in part, on the weight and height of the donor, the target plasma amount to collect calculated based, at least in part, on the donor's body mass index.

164. *See* §X.C.2.i (claim 10).

4. Claim 26

i. The 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 target plasma amount to collect calculated based, at least in part, on the donor's body mass index.

165. *See* §§X.C.2.i, X.C.3.i (claims 10, 16).

D. Ground IV: Fletcher-Haynes in view of Lavender and in further view of Neyrinck renders obvious claim 2.

1. It would have been obvious for a POSITA to further modify the Fletcher-Haynes and Lavender system with Neyrinck

166. As I discuss in §§X.B.1, X.C.1 (Grounds II-III), a POSITA would have been motivated to combine Fletcher-Haynes with Lavender and Fletcher-Haynes with Neyrinck, respectively, and would have had a reasonable expectation of success in making the proposed combination. A POSITA would have found it obvious and would have been motivated to incorporate the teachings of Neyrinck into the Fletcher-Haynes/Lavender system and would have had a reasonable expectation of success because 1) all references relate to the same well-known technologies, 2) apply substantially similar techniques to achieve similar results, and 3) the intended functionality of Fletcher-Haynes/Lavender system would remain substantially the same in the proposed combination adding Neyrinck.

167. First, as I discuss above in §§X.B.1, X.C.1 (Grounds II-III), Fletcher-Haynes, Lavender, and Neyrinck relate to plasma apheresis.

168. Second, as I discuss above in §§X.B.1, X.C.1 (Grounds II-III), Fletcher-Haynes, Lavender, and Neyrinck use substantially similar techniques to achieve similar results. Fletcher-Haynes discloses "processing biological data such as height, weight, gender, and platelet pre-count or hematocrit" to determine a target collection volume for "a multitude of donors with differing physiologies, each being subject to potential variations in collection procedures." EX1005, 1:48-59, 2:15-19. Neyrinck and Lavender similarly rely on using donor-specific information to determine a safe and effective plasma collection volume. EX1004, 3:26-28; EX1006, p.38. Lavender calculates the donor's circulating plasma volume as 5% of body weight and collects 18% of that volume. EX1004, 1:12-13, 22:35-46. Neyrinck similarly utilizes the donor's data such as weight and height to calculate TBV and uses the calculated TBV and hematocrit to calculate total plasma volume. EX1005, p.39-40.

169. Lastly, as I discuss in §X.B.1, incorporating Fletcher-Haynes' prediction algorithm into Lavender's main loop would have been a similarly minor software change for which a POSITA would have had a reasonable expectation of success. As I discuss in §X.C.1, replacing Fletcher-Haynes' calculation of total blood volume with Neyrinck's calculation based on donor BMI would have been a routine

software change that would not have altered Fletcher-Haynes' functionality. Likewise, replacing Fletcher-Haynes' calculation of total blood volume with Neyrinck's calculation based on donor BMI within a structure like Lavender's Main Loop would have been a similarly minor routine change.

2. Claim 2

i. The method according to claim 1, further comprising: calculating the donor's body mass index based, at least in part on the weight and the height of the donor, the target plasma amount to collect calculated based, at least in part, on the donor's body mass index

170. Fletcher-Haynes in view of Lavender and Neyrinck renders obvious claim 2. *See* §§X.C.2.i, X.C.3.i, X.C.4.i (claims 10, 16, 26). As I discuss in §X.D.1, a POSITA would have been successful incorporating Neyrinck's calculation of total blood volume into Fletcher-Haynes' prediction algorithm and would have had a reasonable expectation of success in doing so in the Fletcher-Haynes/Lavender system.

XI. GROUND V: LACK OF PATENT ELIGIBLE SUBJECT MATTER

171. Because patent eligibility is a question of law, I do not provide any opinions on patent eligibility. I have, however, been asked to provide my opinions as a POSITA regarding issues that may underlie the question of patent eligibility. Because many of these opinions relate to the conventionality of equipment, systems,

and methods discussed in the ’204 Patent, these opinions are discussed in my Background on Plasma Apheresis Section.

XII. GROUND VI: CLAIMS 3, 6, 12, 20-21, AND 28-29 LACK SUPPORT IN THE ’204 PATENT SPECIFICATION

172. I understand that the ’204 patent is a continuation-in-part of the ’652 patent and a continuation of the ’416 patent. But many of the ’204 patent’s claims barely resemble the specification it shares with these patents. Thus, Haemonetics’ claims fail to meet the written description requirement.

1. Disclosure of the Purported Invention

173. As I discuss above, Haemonetics’ purported invention is a blood processing system that continues collecting plasma until reaching a target volume of pure plasma. EX1001, 7:17-19. To do that, Haemonetics purportedly tracks the amount of pure plasma in the container while blood is being drawn and checks whether the amount of pure plasma equals a target volume of pure plasma. See EX1001, Fig. 5. Figure 5 of the ’204 patent illustrates the steps allegedly performed by Haemonetics’ patented system.

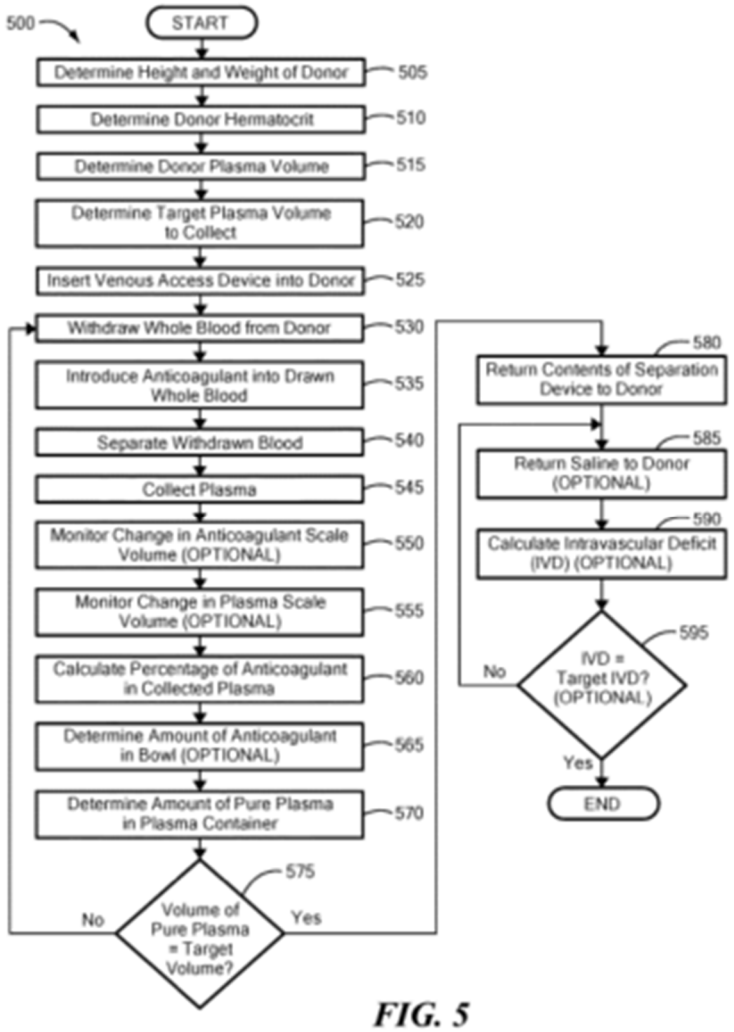


FIG. 5

174. As shown in Figure 5, the technician or system determines a donor's weight, height, and hematocrit to calculate a total plasma volume to collect before withdrawing blood. Then, the method enters a loop (steps 530-570) that continues until "volume of pure plasma = target volume." EX1001, Fig. 5. The technician or the system withdraws whole blood, introduces anticoagulant into withdrawn blood, collects plasma, calculates the percentage of anticoagulant in collected plasma, and

determines the amount of pure plasma in the plasma container. EX1005, 11:58-12:8. Once plasma collection is complete, saline is returned to the donor to compensate for lost plasma and "reduce any adverse reactions that the donor may experience." EX1001, 17:41-49.

B. Argument

175. Claims 3, 6, 12, 14, 19-20, and 28-29 recite limitations that lack written description support in the '204 patent. For example, these claims, as I discuss further below, include claim limitations that recite basic apheresis equipment that allegedly **calculates an optimized, safe target plasma donation volume**, and measures/calculates target volumes of **anticoagulated plasma**. None of these categories have sufficient written description support in the '204 patent's specification.

1. There is no written description support for "calculating an optimized, safe target plasma donation volume"

176. Claims 3, 12, 20, and 29, which require calculating an optimized, safe target plasma donation volume lack adequate written description support. The only time that the words "optimized," "safe," or any variants thereof appear in the '204 patent are in claims 3, 12, 20, and 29. There is no mention of what optimization entails — whether it refers to maximizing plasma yield, minimizing donor risk, or balancing both. That is because the specification provides only general guidance on

calculating plasma volumes based on donor characteristics such as weight, height, and hematocrit, but it does not explain how these calculations result in a plasma volume that is "optimized" or "safe."

177. The '204 patent identifies various side effects that may occur during a plasma donation procedure, including falling, fainting, light-headedness, vasovagal reactions, but the '204 patent does not distinguish whether and when these side effects are ***unsafe clinical risks*** for the donor. *See* EX1001, 17:45-49. Further, the '204 patent describes that it is the saline return, not the removal of a specific target volume of pure plasma, that minimizes these adverse side effects. EX1001, 17:45-49. Thus, this disconnect further underscores the lack of written description support for the claimed "optimized, safe" target plasma volume.

2. Limitations requiring an anticoagulated plasma target volume are unsupported.

178. Claims 6, 14, 19, and 23, which require calculating a target volume of anticoagulated plasma, lack adequate written description support.

179. Haemonetics uses the term "plasma product" sparsely in its specification: once to describe the technical field, later to distinguish the alleged invention over prior art systems, and finally in discussing saline return in prior art systems. EX1001, 1:39-41, 17:4-8, 17:34-39. Figure 5, which shows the purported invention, does not reference plasma product.

180. First, Haemonetics' disclosure that the field of the invention is collecting "a plasma product" does not support claim limitations reciting measuring/calculating target or current plasma product volumes.

181. Further, the reason for these sparse disclosures is that the '204 patent teaches away from collecting a "plasma product" that is not "pure plasma." "[I]llustrative embodiments of" Haemonetics' purported invention include only a system for "collecting a target volume of pure plasma." EX1001, 7:17:19. Haemonetics' claimed system collects plasma until a collected volume reaches a target volume of pure plasma because doing so offers the purported improvement of "collect[ing] a greater volume of pure plasma collected as compared to prior art systems that collect based on the volume of the plasma product." EX1001, 10:29-31; 11:13-18. 17:34-39. Thus, the focus of the patent is ***pure plasma*** collection, not plasma product collection.

182. Additionally, Haemonetics' claim 1 broadens the scope of its claims to include calculating a "plasma product" target volume using "and/or" language. EX1001, claim 1. Specifically, it recites "to determine a target volume for plasma product and/or raw plasma." In doing so, Haemonetics claims what the '204 patent identifies as prior art (calculating a volume of plasma product) in addition to its purported invention (calculating a volume of pure plasma). EX1001, 12:64-13:2.

Haemonetics' disclosure of the prior art calculating a volume of plasma product is insufficient to provide written description support for its claimed invention, which is focused on calculating pure plasma volumes, also calculating plasma product volumes.

183. Simply put, Haemonetics' claimed system does not calculate a target volume for plasma product, rendering any claims that calculate a target volume of anticoagulated plasma invalid for a lack of written description.

E. Ground VII: Claims 3, 8, 12, 20, 23, and 29 Are Indefinite Under Section 112(b).

1. Claims that calculate a target plasma amount that is an optimized, safe amount are indefinite.

184. Claims 3, 12, 20, and 29, which require calculating a target plasma amount that is an optimized, safe amount are indefinite. As a threshold matter, neither the specification, nor the prosecution history offer any clarity regarding the meaning of an "optimized, safe" target plasma amount. *See generally* EX1002, §XI.B.2.i (Lack of Written Description). Because neither the specification nor the prosecution history offer any guidance on the meaning of the term "optimized safe" amount, it is unclear to a POSITA whether the "optimization" refers to the volume of plasma that is collected from the donation procedure, the donor's overall safety, or both.

185. Assuming that the claimed "optimization" refers to volume, a POSITA would not understand what an optimized plasma collection amount is because the specification gives contradictory guidance on calculating an optimized volume. The beginning of the specification suggests that "[t]he target volume of pure plasma may be based, at least in part, on the weight of the donor" and that a "a target volume of pure plasma is … a limit prescribed by the FDA or similar governing body" but the end of the specification suggests that the FDA nomogram for plasma collection which is "based solely on the weight of the donor" is not optimized. EX1001, 11:65-12:8, 3:9-10, 17:4-29. The '204 patent also mentions a range of percentages of plasma to collect (e.g., 26.5% to 30%) but also acknowledges that these percentages may vary and be "preset from the factory" or "input directly into the system." EX1001, 14:14-20. Immediately thereafter, the '204 patent suggests that "the target percentage may be below 26.5% or above 30%, indicating that the range of 26.5% to 30%, or other machine-selected plasma volume, is not optimal. EX1001, 14:19-20. This wide variability in the target volume of plasma to collect from the donor's total plasma volume undermines the notion of a fixed, optimized amount to collect. If the target percentage can be arbitrarily selected, then the scope of the claimed "optimized safe amount" becomes entirely dependent on technician or manufacturer discretion, which is impermissibly vague.

186. If the claims refer to optimizing the safety of a target collection volume, then the term "safe" is also indefinite. The specification discusses possible "adverse reactions that the donor may experience (e.g., falling, fainting, light-headedness, vasovagal reactions)" but discusses "tailoring the saline return" and "achieving isovolemia"—as opposed to calculating a target plasma donation amount— that minimizes such adverse reactions. EX1001, 17:34-49. In other words, the only "safe" plasma target donation volume is 0 mL because it is the removal of blood from the patient that reduces donor safety and *all* target donation volumes above 0 mL are unsafe. That is because the side effects of falling, fainting, light-headedness, or vasovagal reactions are ever present when removing plasma from a donor. Moreover, neither the specification nor the prosecution history clarify which of the side effects listed in the specification—falling, fainting, light-headedness, or vasovagal reactions—are forms of donor discomfort or side effects cross in the realm of clinical unsafety. If a safe plasma donation amount means "FDA approved," then the specification does not describe how to achieve such FDA clinical approval.

187. Lastly, if an "optimized, safe" plasma target donation volume means optimizing both safety and volume together, then the claims are still indefinite. There is no guidance on how much to reduce a target plasma volume to reduce to minimize side effects, *e.g.*, such as fainting or falling. Similarly, the specification does not

describe when it is better to further increase the target plasma donation volume at the cost of a greater risk of side effects, *e.g.*, more lightheadedness.

2. Claims requiring the flow through the first line being controlled by a first pump are indefinite

188. A POSITA would not understand how to design the claimed apheresis system having "the flow through the first line being controlled by a first pump." First, the claim fails to clarify whether the "first pump" controls the draw flow (from the donor to the separation device), the return flow (from the separation device back to the donor), or both. This is particularly problematic given that the claimed "first line" serves both functions. Second, the specification describes multiple components that influence flow, including valves and a controller, raising uncertainty as to whether the claimed pump is the sole or primary means of flow control through the first line. Likewise, "controlled" is a broad and undefined term that could encompass a range of mechanisms—such as regulation of flow rate, initiation or cessation of flow, pressure modulation, or directional control—none of which are clearly specified in the claim language or adequately supported in the specification. Third, the claim language recites a function—controlling flow—without providing sufficient structural detail such that a POSITA would understand the specific flow control the claimed pump performs, *e.g.*, whether it is directional, volumetric, or pressure-based, or whether the claimed pump is the primary or sole means of flow

control through the first line. Without a clear delineation of the pump's flow control, a person of ordinary skill in the art would not be able to design the claimed apheresis system with the claimed pump.

F. Claims 3, 12, 20, and 29 Are Not Enabled Under Section 112(a).

189. I understand that the *Wands* factors are used to assess whether undue experimentation is required, which include: (1) the quantity of experimentation necessary; (2) the amount of direction or guidance provided; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. For substantially the same reasons described in §XI.B.2.i and §XI.C, claims 3, 12, 20, and 29 require undue experimentation to enable.

190. As a threshold matter, the breadth of the claims (Factor 8) is substantial: it covers any plasma collection process that results in an "optimized safe amount" tailored to a donor, yet the specification provides no clear definition or boundaries for what "optimized" or "safe" mean. Similarly, the nature of the invention (Factor 4) involves medical procedures with patient-specific variables, where safety and optimization are governed by clinical standards and regulatory limits. These are complex and context-dependent concepts that require precise guidance, which, as I

discuss in Section X.B.2.i, the ’204 patent fails to provide. This is true even though POSITAs in the field of plasma apheresis have a relatively higher skill level than those of other fields (Factor 6).

191. Since the specification and prosecution history provide no guidance as to the meaning of “optimized” or “safe” target plasma donation volumes (Factor 2)—and optimal donation volume and safety are subjective to each donor—a POSITA would need a high amount of experimentation (Factor 1) to enable claims 3, 12, 20, and 29 of the ’204 patent. Specifically, a POSITA would need to conduct clinical trials or develop their own criteria to determine what plasma volume is both optimized and safe for different donor profiles.

192. As I discuss in §XI.C, the specification gives contradictory examples of target plasma volumes (Factor 3), suggesting that there is no such optimal volume. The same is true for donor safety, as the patent suggests removing any target volume of plasma may always result in “falling, fainting, light-headedness, vasovagal reactions” unless an amount of saline is returned to the donor to compensate for blood loss.

193. Finally, the predictability or unpredictability of the art (Factor 7) weighs heavily against enablement, as human physiology varies widely. What is safe or

optimal for one donor may not be for another. Without concrete guidance, the claim invites trial-and-error experimentation.

194. Therefore, it is my opinion that all the *Wands* factors support a finding that claims 3, 12, 20, and 29 require undue experimentation.

XIII. AVAILABILITY FOR CROSS-EXAMINATION

195. 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.

XIV. RIGHT TO SUPPLEMENT

196. 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.

XV. JURAT

197. 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 21, 2025	

Terumo v. Haemonetics - PGR2026-00006
Petitioner Terumo Exhibit 1003-0095