UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TERUMO BCT,

Petitioner,

v.

HAEMONETICS CORP.,

Patent Owner,

Patent No. 10,758,652 to Ragusa
Issue Date: September 1, 2020

Inter Partes Review No.: IPR2025-01391

Corrected Declaration of Dr. Gary D. Fletcher

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3. Claim 6: A method according to claim 1, further comprising: monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection container based, at least in part, on the monitored weight of collected plasma component 45

4. Claim 8: A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor. 45

5. Claim 10: A method according to claim 1, further comprising returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line. 46

6. Claim 11 48

7. Claim 16: A system according to claim 11, a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma component based, at least in part, on the monitored volume of collected plasma component. 49

8. Claim 17: A system according to claim 11, a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma component based, at least in part, on the monitored weight of collected plasma component. 50

9. Claim 19: A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the subject. 50

B. Ground 2: Claims 1, 3, 5, 6, 8, 10-12, 14, 16-17, and 19 are anticipated or rendered obvious by Lavender 50

1. Claim 1 50

2. Claim 3: A method according to claim 1, further comprising: determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the number of rotations of the anticoagulant pump. 60

3. Claim 5: A method according to claim 1, further comprising: monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection

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container based, at least in part, on the monitored volume of collected plasma component. 62

4. Claim 6: A method according to claim 1, further comprising: monitoring a weight of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection container based, at least in part, on the monitored weight of collected plasma component 63

5. Claim 8: A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor. 63

6. Claim 10: A method according to claim 1, further comprising returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line. 64

7. Claim 11 65

8. Claim 12: A system according to claim 11, wherein the volume of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit. 67

9. Claim 14: A system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the number of rotations of the anticoagulant pump. 71

10. Claim 16: A system according to claim 11, a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma component based, at least in part, on the monitored volume of collected plasma component. 72

11. Claim 17: A system according to claim 11, a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma component based, at least in part, on the monitored weight of collected plasma component. 72

12. Claim 19: A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the subject. 72

C. Ground 3: Claims 2, 9, 13, and 20 are obvious over Takagi in view of Min 72

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1. Reasons to Combine Takagi and Min 72

2. Claim 2: A method according to claim 1, further comprising: determining a change in volume within an anticoagulant container, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the change in volume within the anticoagulant container. 75

3. Claim 9: A method according to claim 1, wherein the volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step. 77

4. Claim 13: A system according to claim 11, an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant source based on the measured weight of the anticoagulant source, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the change in volume within the anticoagulant source. 79

5. Claim 20: A system according to claim 11, wherein the volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step. 79

D. Ground 4: Claims 7 and 18 are obvious over Lavender in view of Takagi, Headley, and Barrett 79

1. Claim 7: A method according to claim 1, further comprising: wherein step (b) includes monitoring a volume of red blood cells collected within the blood component separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the donor. 79

2. Claim 18: A system according to claim 11, an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood component separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the subject. 84

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E. Ground 5: Claims 4 and 15 are obvious over Lavender in view of Takagi, Min, and Turgut 85

1. Claim 4: A method according to claim 1, further comprising: determining a volume of anticoagulant within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device. 86

2. Claim 15: A system according to claim 11, an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device. 88

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EXHIBIT LIST

Exhibit	Reference
1001	U.S. Patent No. 10,758,652 ("'652 patent")
1002	File History of the '652 patent
1003	Declaration of Dr. Gary D. Fletcher in Support of Petition
1004	Japanese Patent Publication No. JP 2002-282352 A including certified English translation and declaration by Japanese translator ("Takagi")
1005	U.S. Patent No. 4,898,675 ("Lavender")
1006	U.S. Patent No. 8,075,468 ("Min")
1007	U.S. Patent Publication No. 2003/0125881 ("Ryan")
1008	U.S. Patent No. 9,370,324 ("Barrett")
1009	U.S. Patent No. 6,296,602 ("Headley")
1010	"Membrane versus centrifuge-based therapeutic plasma exchange: a randomized prospective crossover study," Carsten Hafer et al., Int. Urol. Nephrol (2016) 48:133-138; Springer Science+Business Media Dordrecht 2015.
1011	U.S. Patent Publication No. 2017/0029762 ("Turgut")
1012	"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.
1013	Bruce C. McLeod, MD, et al., "Apheresis: Principles and Practice," 3rd Edition, AABB Press 2010.
1014	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
1015	Curriculum Vitae ("CV") of Dr. Gary D. Fletcher
1016	U.S. Patent Publication No. 2012/0175313 ("Barry")
1017	Search Disclosure Declaration (Filing Party and Board Only)
1018	Redacted Search Disclosure Declaration

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I. INTRODUCTION

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

2. I have been retained as a technical expert by counsel on behalf of Terumo BCT, Inc. ("Petitioner"). I understand that Petitioner is requesting that the Patent Trial and Appeal Board institute an *Inter Partes* review ("IPR") proceeding of U.S. Patent No. 10,758,652 ("the '652 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 1–20 (the "challenged claims") of the '652 patent. My opinions and the bases for my opinions are set forth below. My opinions are based on my education and experience.

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

5. I am not, and never have been, an employee of Petitioner. I have no financial interest in either party or in the outcome of this proceeding. I am being

compensated for my work as an expert on an hourly basis, for all tasks involved. My compensation is not dependent on the outcome of these proceedings or on the content of my opinions. I will not receive any added compensation based on the outcome of any IPR or other proceeding involving the ’652 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 EX1015 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

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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 EX1015.

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,

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

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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 EX1015.

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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 at the time of the alleged invention of the ’652 patent (“POSITA”; refer to §VI, below) 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 ’652 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 understand to be the earliest effective filing date of the claims for purposes of this analysis. I have

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considered the materials referenced herein, including the '652 patent (EX1001), the prosecution history (EX1002) of the '652 Patent, and the following materials:

- Japanese Patent Publication No. JP 2002-282352 A and English translation ("Takagi," EX. 1004)
- U.S. Patent No. 4,898,675 to Lavender ("Lavender," EX. 1005);
- U.S. Patent No. 8,075,468 to Min *et al.* ("Min," EX. 1006);
- U.S. Patent Publication No. 2003/0125881 to Ryan ("Ryan," EX. 1007);
- U.S. Patent No. 9,370,324 to Barret *et al.* ("Barrett," EX. 1008);
- U.S. Patent No. 6,296,602 to Headley ("Headley," EX. 1009);
- "Membrane versus centrifuge-based therapeutic plasma exchange: a randomized prospective crossover study," Carsten Hafer et al., Int. Urol. Nephrol (2016) 48:133-138; Springer Science+Business Media Dordrecht 2015. (EX. 1010);
- U.S. Patent Publication No. 2017/0029762 ("Turgot," EX. 1011).)
- "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. (EX. 1012);

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- Bruce C. McLeod, MD, et al., "Apheresis: Principles and Practice," 3rd Edition, AABB Press 2010. (EX. 1013);
- 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 (EX. 1014); and
- U.S. Patent Publication No. 2012/0175313 to Barry *et al.* ("Barry," EX. 1016).

16. I have considered these materials through the lens of a POSITA, which is discussed further in §§V and VI (below) related to the '652 Patent as of the effective filing date, and I have done so during my review of these materials.

IV. SUMMARY OF MY OPINIONS

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

- Claims 1, 5, 6, 8, 10, 11, 16, 17, and 19 are anticipated by or obvious over Takagi;

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- Claims 1, 3, 5, 6, 8, 10-12, 14, 16-17, and 19 are anticipated by or obvious over Lavender;
- Claims 2, 9, 13, and 20 are obvious over Takagi and Min;
- Claims 7 and 18 are obvious over Lavender in view of Takagi, Headley, and Barrett; and
- Claims 4 and 15 are obvious over Lavender in view of Takagi, Min, and Turgut.

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

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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

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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.

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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;

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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

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invention, any long-felt but unsolved need in the art that was satisfied by the alleged invention, the failure of others to make the alleged invention, praise of the alleged invention by those having ordinary skill in the art, and copying of the alleged invention by others in the field. I further understand that there must be a nexus— a connection—between any such secondary considerations and the alleged invention. I also understand that contemporaneous and independent invention by others is a secondary consideration tending to show obviousness.

VI. Level Of Ordinary Skill

29. In my opinion, a POSITA would have had, as of what I understand to be the earliest claimed filing date of May 30, 2017, a bachelor's degree in biomedical engineering, or a related field, such as physical sciences, physics, computer engineering, electrical engineering, or the like, and a minimum of two to three years of experience related to blood separation devices or blood processing devices. A higher level of education or specific skill might make up for less experience, and vice versa.

VII. Background on Plasmapheresis

30. The '652 patent relates to apheresis systems, specifically apparatuses and methods for plasmapheresis, which is also called plasma apheresis—the

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extracorporeal separation and collection of plasma from whole blood, with cellular components returned to the donor.

31. Plasmapheresis, also known as plasma exchange or therapeutic plasma exchange, has been a clinical procedure since the 1960s. EX1013, Chapter 1: Development of Apheresis Instrumentation. It selectively removes plasma and returns cellular components along with replacement fluid using centrifugation or membrane filtration. EX1010. The earliest methodologies emerged from continuous centrifugation techniques in the 1960s, evolving to membrane-based and automated extraction systems. Early systems typically required large volumes of anticoagulants, continuous supervision by trained personnel, and bulky, non-portable equipment. Over time, manufacturers have introduced increasingly sophisticated machines that automate component separation, enhance flow control, monitor patient safety, and optimize plasma yield.

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

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33. In automated plasmapheresis, whole blood is drawn from the donor, mixed at a specified ratio with anticoagulant, and then separated into anticoagulated plasma and red blood cells and other cellular components. Once a target volume of anticoagulated plasma has been collected, the withdrawal of whole blood from the donor ceases, and the red blood cells and other cellular components are returned to the donor. EX1013, Chapter 4: Current Instrumentation of Apheresis.

34. The FDA issued guidelines for registered blood collection centers as to the volume of plasma that may be collected during plasmapheresis in order to improve the consistency of procedures for manufacturing source plasma, and to minimize the opportunity for staff error. EX1012. 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

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maximum collection volume for the total of the plasma plus the anticoagulant for a particular donor. EX1012.

35. At the time the ’652 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. EX1013, 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. EX1013, p. 129 (Table 6-3). Furthermore, advanced plasmapheresis systems used real-time sensor feedback (e.g., pressure, volume, optical detection) to

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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 '124 patent. *See, e.g.*, EX1004.

VIII. '652 Patent Overview

A. The '652 Patent is Directed to Plasma Apheresis

36. The '652 patent, which recently issued on September 1, 2020, relates to a "system and method for collecting plasma" in blood apheresis systems. EX1001, Title, 1:6-8. "Apheresis is a procedure in which individual blood components," e.g., plasma and red blood cells, "can be separated and collected from whole blood." EX1001, 1:12-14. The '652 patent specifically relates to plasma apheresis, or plasma

[1] *See* EX1013, 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.*, EX1013, p. 14, "The pump flow rates—and, thereby, the component collection—are controlled by the microprocessor in response to the optical monitor."

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collection. Figure 3 of the '652 patent shows one embodiment of a plasma apheresis system.

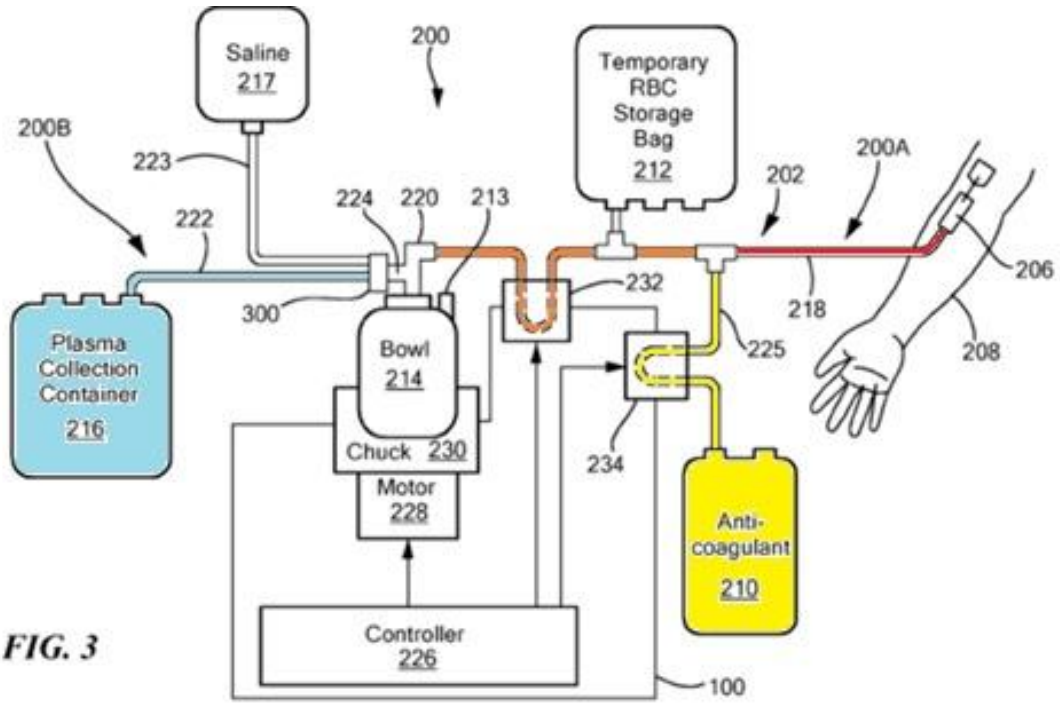


FIG. 3

EX1001, Fig. 3.

37. Plasma apheresis involves withdrawing whole blood from a donor's arm using venous access device 206. EX1001, 5:14-16. Pump 232 "causes the whole blood to be drawn from the donor" through an inlet line 218 (shown in red) and pump 234 adds a fixed amount of anticoagulant "into the whole blood" through "[a]n anticoagulant line" 225 (shown in yellow) connected "to the inlet line." EX1001, 6:13-16, 7:20-26. Anticoagulant is introduced in fixed proportions to the whole

blood drawn from the donor to prevent blood clotting in the draw line. *See* EX1012. "[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, 7:43-47.

38. Then, the mixture (shown in 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, 4:52-61, 6:40-45. The donor's plasma, i.e., pure plasma, along with anticoagulant introduced during the collection process, exits the blood component separation device and is collected and stored in a collection container (e.g., a bag, shown in blue above). EX1001, 1:55-62, 5:14-24. The combination of anticoagulant and pure plasma is known as anticoagulated plasma or plasma product. EX1001, 9:57-58.

39. The FDA established guidelines regarding how much plasma any individual donor is able to donate. See EX1012. These guidelines consider donor parameters, like weight, hematocrit, and sex. *See* EX1012.

A. The '652 Patent's Purported Invention

40. The '652 patent purports to solve problems associated with "determin[ing] the total volume of plasma that has been collected" from a donor

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after the withdrawn whole blood is mixed with anticoagulant. EX1001, 1:38-44. The '652 patent purports to solve these problems by taking into consideration a donor's hematocrit level and the amount of anticoagulant added into the system. EX1001, 1:48-2:6; 4:8-19.

41. Each donor has a different hematocrit level, which affects the amount of plasma in the donor's whole blood. EX1001, 7:55-57. The differing levels of hematocrit affect the volume of anticoagulant in a plasma collection bag ("anticoagulant volume"). EX1001, 7:64-67. Given this variability, the '652 patent discloses that controller 226 may use the % AC equation below, which includes a predetermined ratio of anticoagulant to anticoagulated whole-blood and the donor's hematocrit to calculate the percentage of anticoagulant in the plasma container. EX1001, 8:9-46. Specifically, in % AC below, "AC" is the inverse of the predetermined ratio of anticoagulant per unit of anticoagulated whole blood (e.g., "AC" would be 16 if the ratio of anticoagulant to anticoagulated whole blood was 1:16) and Hct_D is the donor's hematocrit. EX1001, 8:9-46. Anticoagulated whole blood is extracted blood mixed with anticoagulant.

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

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42. The ’652 patent discloses that the controller also monitors the weight of the collection container using a weight sensor and uses it to determine the total volume of liquid in the collection container. EX1001, 7:15-17, 7:50-54. The controller uses the total volume of liquid in the collection container for two calculations: (1) calculating the anticoagulant volume and (2) calculating the volume of pure plasma in the collection container. EX1001, 8:1-9:40. The controller calculates the anticoagulant volume by multiplying the anticoagulant percentage (“% AC”) by the total volume of liquid in the container. EX1001, 8:47-64. The ’652 patent then calculates the volume of pure plasma in the collection container by subtracting the anticoagulant volume from the total volume of liquid in the collection container. EX1001, 8:47-64.

43. The ’652 patent also discloses two alternative methods of determining the amount of anticoagulant in the collection bag that do not consider a donor’s hematocrit. These include determining the anticoagulant in the collection bag by: (i) monitoring the volume of anticoagulant added to the system based on the number of rotations of the anticoagulant pump, and (ii) measuring the change in weight of the anticoagulant container. EX1001, 8:29-64. Something to note is that “[b]ecause the osmolarity of the red blood cells prevents the anticoagulant from mixing with it, essentially all of the anticoagulant exits the bowl 214 and is collected within the

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plasma collection container 216 along with the plasma." EX1001 at 8:18-23. Under this assumption, subtracting the volume of anticoagulant added to the system from the total volume in the collection container provides an estimate of the volume of pure plasma within the collection container. EX1001 at 8:18-23; 9:25-40. In both of these methods disclosed in the '652 patent, the volume of anticoagulant that is added is then used to calculate the volume of pure plasma collected in the plasma collection container by subtracting the added anticoagulant volume from the total volume in the collection container. EX1001, 8: 18-23, 8:37-46, 9:25-40.

44. Of the three methods I discussed above, only the first, which is based on the predetermined ratio of anticoagulant to anticoagulated whole blood, considers the donor's hematocrit. That method does not, however, use an amount of anticoagulant collected within the plasma collection container or supplied to the system to determine a percentage of anticoagulant within the collected plasma. EX1001 at 10:2-6.

45. In the '652 patent, each method to determine the volume of pure plasma is repeated "until a target volume of pure plasma is collected in the plasma collection container," e.g., the volume set by FDA regulation. EX1001, 8:61-64. When the system reaches a target volume of pure plasma, the controller "stops the draw of whole blood from the subject and reverses the direction of the blood … to

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draw the RBCs (and other components)" from the blood component separation device back to the donor. EX1001, 9:2-8.

46. As I will explain below, these concepts were well known as of the priority date of the '652 patent.

IX. Prior Art Overview

A. Overview of Takagi

47. Takagi discloses a blood component collecting device for collecting a blood component, such as plasma. EX1004, Abstract. Takagi recognized the need to track the volume of pure plasma collected during a plasma collection procedure to better track the amount of pure plasma collected and increase procedure safety. EX1004, ¶0153.

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48. Takagi's blood component collection device 1, shown below in Figure 1, withdraws a donor's blood and uses centrifuge 20 to separate it into components. EX1004, ¶0021.

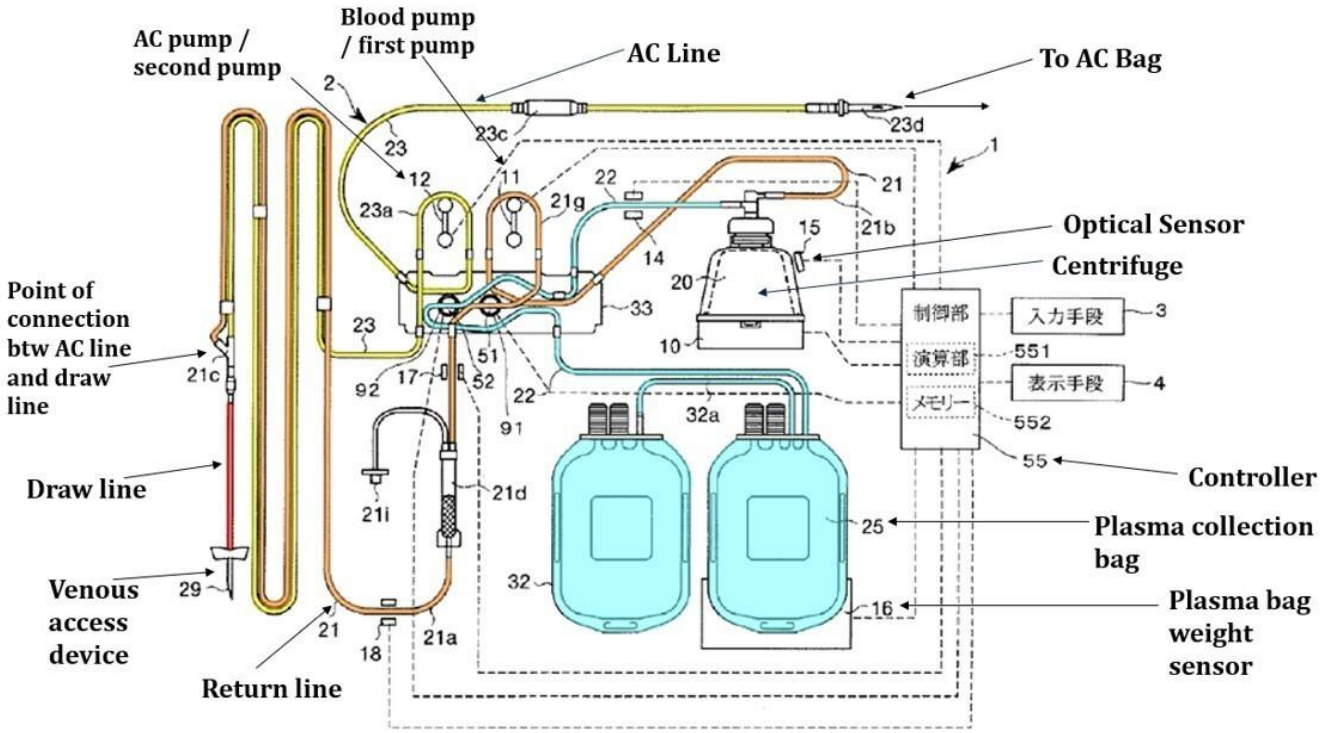


FIG. 1

EX1004, FIG. 1 (annotated).

49. First line 21 receives withdrawn whole blood from the donor (e.g. through needle 29), and third line 23, connected to first line 21, is used to inject anticoagulant into the incoming whole blood. EX1004, ¶¶0022-0023. The anticoagulant and whole blood mixture is pumped through the remaining section of first line 21 to centrifuge 20. Id. Centrifuge 20 separates the plasma from other blood components, and second line 22 connects centrifuge 20 with plasma collection bag

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25 that collects the separated plasma. EX1004, ¶¶0021-0023. First fluid supplying pump 11 pumps fluid through first line 21, and second fluid supplying pump 12 pumps fluid through the third line 23. EX1004, ¶0023. Takagi uses weight sensor 16 to detect the amount of plasma collected in plasma collection bag 25. EX1004, ¶0055. Control unit 55 controls the operations of centrifuge drive unit 10, first and second fluid supplying pumps 11, 12, and first and second flow path opening/closing means 51, 52 based on detection signals from the components, like weight sensor 16. EX1004, ¶¶0023, 0062, 0112.

50. Before starting a procedure, control unit 55 obtains the "apparent plasma collection amount per cycle" (A), which can be calculated using donor's hematocrit. EX1004, ¶0083. The "apparent plasma collection amount per cycle" (A) is the amount of plasma mixed with anticoagulant collected in the plasma collection bag during the cycle. EX1004, ¶0067. Apparent plasma collection amount per cycle (A) is used to calculate the "anticoagulant admixture amount per cycle" (C), and then both are used to calculate the "true plasma collection amount per cycle" (B) using equation $B = A - C$. EX1004, ¶¶0080-0082; The true plasma collection amount is the plasma by itself after removing the anticoagulant, often referred to as pure plasma amount. EX1004, ¶0067.

51. Blood component collection device 1 then determines the number of

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cycles (E) (iterations) required to collect the "true target plasma collection amount" (D), which is based on donor information (i.e., gender, weight, and height). EX1004, ¶¶0078, 0087-0090. The system then calculated the "true plasma collection amount per cycle in the final cycle" (F) using the true target plasma collection amount (D) and true plasma collection amount per cycle (B). EX1004, ¶¶0092-0093. The "apparent target plasma collection amount" (G) is then calculated using true plasma collection amount per cycle (B), anticoagulant admixture amount (C), and the true plasma collection amount per cycle for the final cycle (F). EX1004, ¶0095.

52. After determining the true target plasma collection amount (D) and apparent target plasma collection amount (G), blood component collection device 1 withdraws blood from the donor, mixes the donor's blood with anticoagulant, delivers the anticoagulated blood into the centrifuge, and collects the anticoagulant-containing plasma (apparent plasma) in the plasma collection bag 25. EX1004, ¶0099. During collection, anticoagulant is added at a predetermined ratio maintained by control unit 55. EX1004, ¶¶ 0101-0104. As blood is drawn from the donor, weight sensor 16 measures the weight of collection bag 25 and control unit 55 uses this weight to calculate the "apparent plasma collection amount" (W) [ml] collected during the collection process. EX1004, ¶0114. Control unit 55 then compares (W) to the "apparent plasma collection amount per cycle" (A) to determine whether (A)

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has been reached. EX1004, ¶0114. If (A) has been reached, collection stops and the control unit determines whether the "true current plasma collection amount" (Z) has reached $M\%$ of the "true target plasma collection amount" (D), or whether the collection has been performed over a certain number of cycles (E). EX1004, ¶¶0117, 0131, 0134-0135.

53. True current plasma collection amount (Z) is calculated using Equation (V-3) below, which adds the "true plasma collection amount collected up through the previous cycle" (Y) (mL) to the "apparent plasma collection amount collected since the start of that cycle" (W) (mL), after subtracting anticoagulant admixture amount (X) (mL) from (W).

Equation (V-3): $Z = Y + (W - X)$

EX1004, ¶0126-127. In other words, control unit 55 determines true current plasma collection amount (Z) by subtracting a volume of anticoagulant (X) in plasma collection bag 25 from apparent plasma collection amount (W). (W) and (Z) are calculated each time the weight of plasma collection bag 25 increases by 1 gram. EX1004, ¶0119. The "true plasma collection amount collected up through the previous cycle" (Y) (mL) has already had the anticoagulant removed in the determination of (Y) in the previous cycle, so Equation (V-3) is effectively taking into account the entire volume of anticoagulant in the plasma collection bag (e.g.

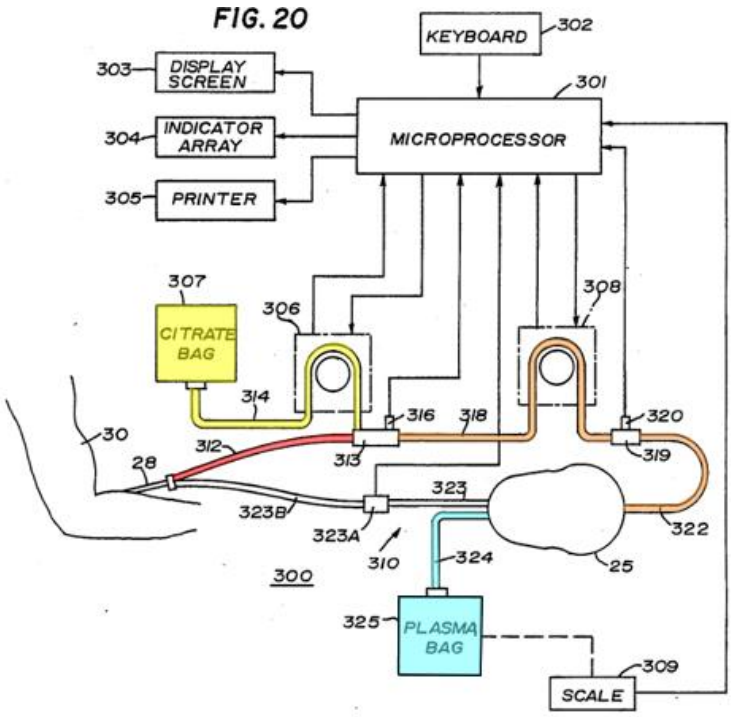
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removing the entire amount of anticoagulant in the plasma collection container) each time Equation (V-3) is calculated.

B. Overview of Lavender

54. Lavender discloses "a system, method and device for continuously fractionating blood in situ." EX1005, Abstract. Like the '652 patent, Lavender recognized the need to track the volume of anticoagulant collected during a plasma collection procedure to, among other things, "accurately, safely and economically collect[ ] plasma from a source of blood." EX1005, 3:26-28.

55. Figure 20 illustrates Lavender's automatic system 300 for fractionating blood. EX1005, 16:34-53.



EX1005, Fig. 20 (color added).

56. In Lavender's system 300, needles or catheter 28 are used to draw whole blood from a donor, which is then mixed with citrate pumped from citrate bag 307. EX1005, 16:60-17:2. Citrate is a blood anticoagulant. EX1005, 16:45-47. The system then pumps the whole blood and anticoagulant mixture to blood fractionator 25, which separates the anticoagulated whole blood into plasma and other blood fractions. EX1005, 5:42-52. The plasma and anticoagulant solution exits the blood separation device through the plasma line and is collected in plasma bag 325. EX1005, 17:14-16.

57. Lavender's system performs several real time calculations during the collection process. These calculations take into account 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 EX1005, 22:35-39, cols. 41, 42. They 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. EX1005, 20:55-68.

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

Variable	Description

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CF (conversion factor)	Predetermined ratio (or percentage) of anticoagulant to incoming plasma
QB	Blood flow from donor
TQB	Total blood flow
HCTD	Donor's hematocrit
QP	Plasma flow
TQP	Total plasma flow
QCP	Citrate pump rate
TQC	Total citrate (anticoagulant) flow
TDPF	Total dilute plasma (total fluid) in the collection container
TPF	Total plasma filtered (pure plasma) volume in the collection container
TCF	Total citrate (anticoagulant) volume in the collection container

59. During the collection process, these variables are used to monitor the amount of plasma collected. For example, plasma flow (QP) is calculated based on the donor's blood flow (QB) and hematocrit (HCTD). EX1005, 41:4-44:42. QP is then used to calculate the citrate pump rate (QCP) by multiplying it by the conversion factor (CF). QCP is used to calculate the total citrate flow (TQC). See EX1005, 41:4-44:42. The total plasma volume in the collection container is

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calculated in real time based on the total volume of fluid in the collection container, determined by the weight of the container, and the plasma dilution factor (PDF). The total citrate volume in the collection container (TCF) is then calculated in real time based on the total plasma volume in the collection container (TPF) and the conversion factor (CF). See EX1005, 41:4-44:42.

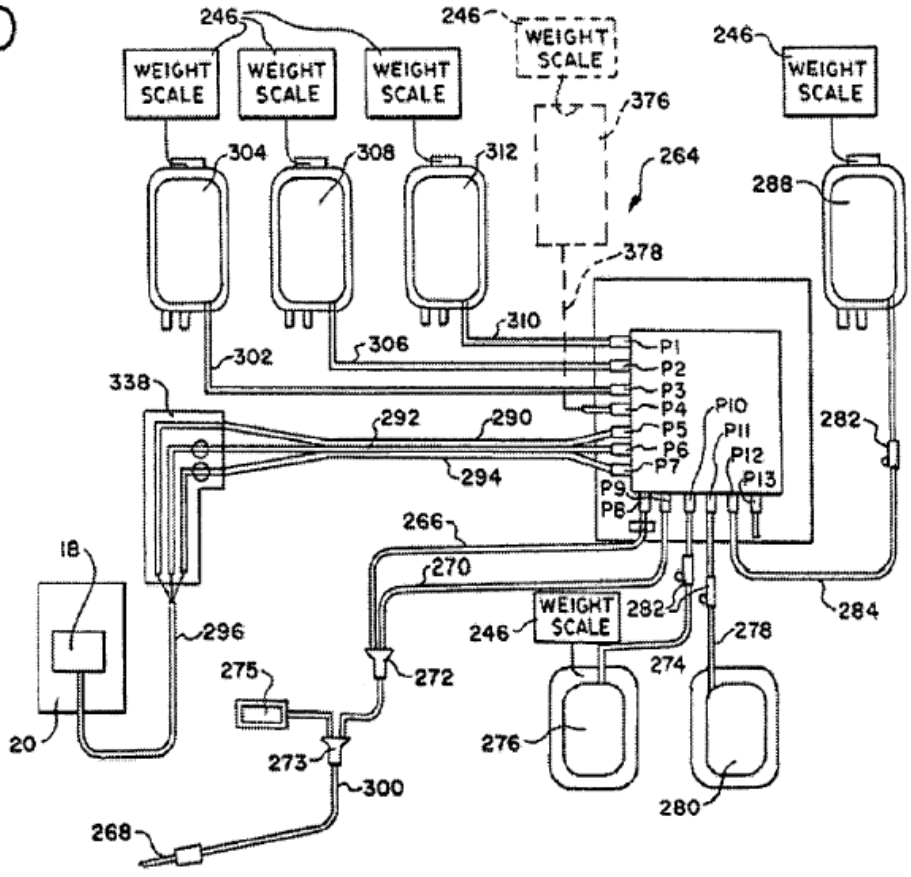
60. In Lavender, the microprocessor repeatedly performs weight measurements and run-time calculations set forth in Lavender's algorithm and displays updated values approximately every two seconds. EX1005, 20:55-68. Lavender's system determines the relationship (ratio) between the pure plasma volume and the anticoagulant volume in the collection container. This is then used to determine the pure plasma volume. Accordingly, Lavender discloses a determination of pure plasma volume based on the volume of anticoagulant. If any additional conversion or calculation is required, a POSITA would readily understand how to convert between the two volumes using the same relationship. Lavender executes a main loop of the algorithm until the total plasma filtered (TPF) in plasma bag 325 is equal to or greater than a determined maximum total plasma volume to collect (MAXPF), as determined using a donor's weight. EX1005, cols. 43-44, claim 33.

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C. Overview of Min

61. Min discloses blood processing systems for separating plasma from whole blood. EX1006, 7:4-8:5. Min teaches plasma collection procedures that include a collection cycle, and pre- and post-collection cycles, which include priming the system's tubing by "convey[ing] a predetermined volume of anticoagulant . . . into the in-process container" during the pre-collection cycle. EX1006, 32:16-18. Figure 10 of Min is a schematic of a system for performing several blood processing procedures, such as plasma collection.

FIG. 10



62. Weigh sensors 246 are used to track weight changes and derive fluid processing volumes, including the volume change in anticoagulant container 276 and plasma collection container 304. EX1006, 11:52-55, 17:17-22.

D. Overview of Barrett

63. Barrett discloses a hemodialysis patient data acquisition and management system for monitoring blood separation procedures, like hemodialysis. EX1008, 4:14-67. Barrett describes several techniques to monitor hematocrit, including ones used for real-time monitoring during hemodialysis. EX1008, 2:23-57. Barrett specifically discloses determining a patient's hematocrit by dividing a blood sample's calculated total red blood cell volume by a total volume of the blood sample. EX1008, 2:45-49.

E. Overview of Headley

64. Headley discloses systems and methods for collecting, from whole blood, platelets suspended in plasma, among other blood components. EX1009, Abstract. Headley's blood separation systems use a centrifuge to separate blood into components and use of an array of optical sensors with a control unit to determine a volume of red blood cells within a blood separation system. EX1009, 4:48-64.

F. Overview of Turgut

65. Turgut discloses separation systems that effectively separate biological material, like blood components, with the help of centrifugal force. EX1011,

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Abstract. Turgut describes blood separation systems that utilize a centrifuge to separate blood into components and describes using a volume detector to determine a total volume of fluid within a blood separation system, such as a separation chamber of a centrifuge used to separate blood into components. EX1011, ¶73.

X. Identification of How the '652 Patent's Claims are Unpatentable

A. Ground 1: Claims 1, 5, 6, 8, 10, 11, 16, 17, and 19 are anticipated or rendered obvious by Takagi

1. Claim 1

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

66. To the extent the preamble is limiting, Takagi discloses "[a] method for collecting plasma." EX1004, ¶¶0001, 0020. Takagi's blood component collecting device "mainly collects plasma as a predetermined blood component." EX1004, ¶0020.

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

67. Takagi determines a weight of a donor. EX1004, ¶¶0063 and 0075. Specifically, "[t]he operator [ ] uses the input means 3 to input information [into blood component collection device 1] related to the donor blood . . . such as gender, weight, height, age, hematocrit value, etc." EX1004, ¶0075.

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

68. Takagi determines a hematocrit of a donor. EX1004, ¶0075. Specifically, "[t]he operator [ ] uses the input means 3 to input information related to the donor blood . . . such as gender, weight, height, age, hematocrit value, etc." EX1004, ¶0075.

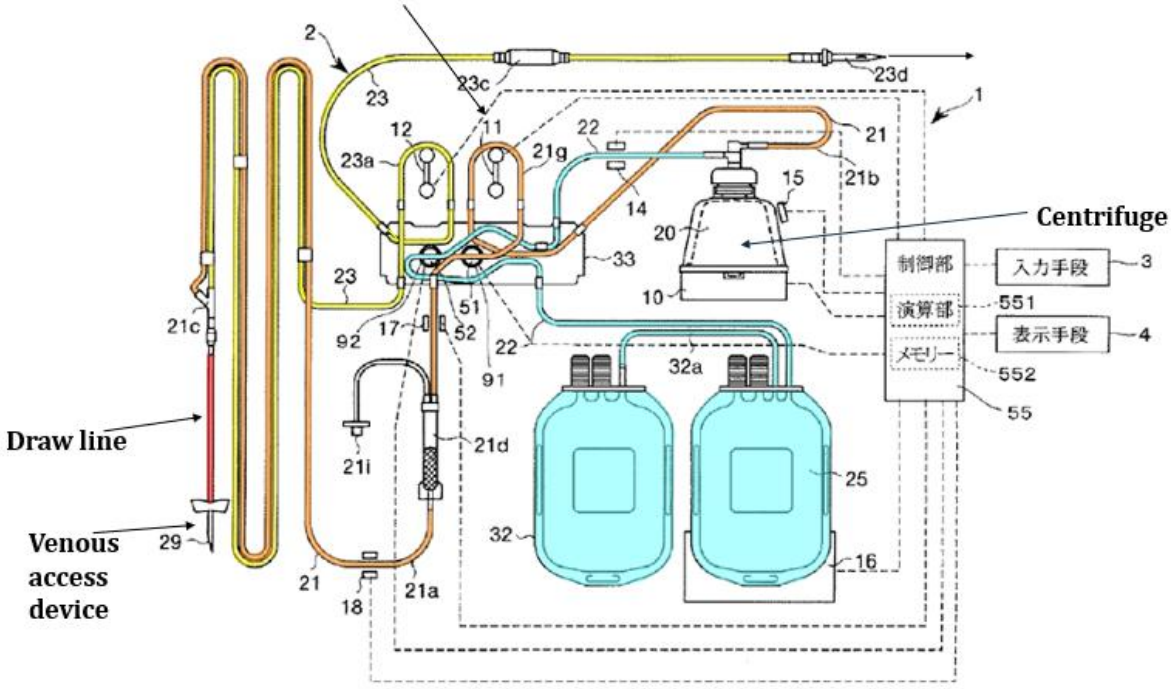
d. 1[c] inserting a venous-access device into the donor;

69. Takagi's collection device 1 uses blood collection needle 29 to puncture a donor's blood vessel and collect blood from the donor. EX1004, ¶0076.

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

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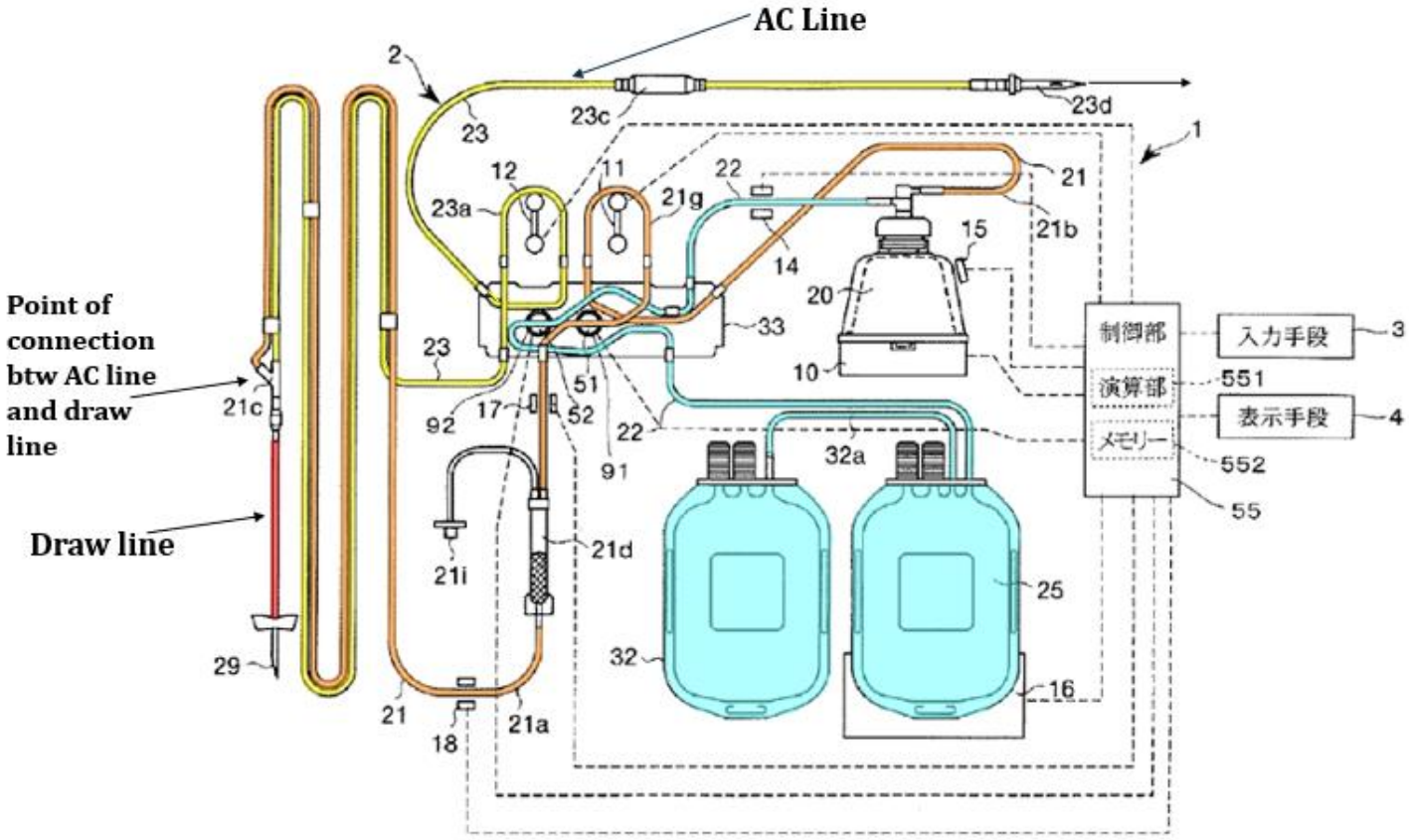
70. Takagi withdraws whole blood through a venous-access device (e.g. needle 29). EX1004, ¶0076. Takagi uses "a first fluid supplying pump 11" which is connected to first line 21, e.g., the draw line, to draw whole blood from the donor into blood component collection device 1. EX1004, ¶¶0023 and 0061. First line 21 is shown connected to centrifuge 20 (a blood component separation device) in Takagi's Figure 1, below.



EX1004, FIG. 1 (annotated).

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

71. In Takagi's collection device 1, "[a] third line 23 and the second liquid delivery pump 12 constitute an anticoagulant supply means for adding [ ] anticoagulant to the blood collected from the donor." EX1004, ¶0024. As shown in Takagi's Figure 1, third line 23 delivers anticoagulant to the withdrawn whole blood in first line 21. EX1004, ¶0024 and Figure 1.



EX1004, FIG. 1 (annotated).

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

72. During the collection process, a donor's whole blood flows into Takagi's centrifuge 20, which separates the whole blood into blood fractions (components), including a plasma component and a component containing red blood cells, white blood cells, and platelets. EX1004, ¶0021.

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

73. Takagi discloses that after centrifuge 20 separates the blood into components, plasma is collected in "a plasma collection bag (blood component collection bag) 25." EX1004, ¶0021.

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

74. During a collection procedure, Takagi discloses adding anticoagulant to the incoming whole blood at a predetermined ratio. EX1004, ¶¶0102-0104. As the donor's blood is drawn, control unit 55 calculates apparent plasma collection amount (W), which is the volume of plasma and anticoagulant mixture collected in collection bag 25 for that cycle using measurements from weight sensor 16. EX1004, ¶¶0114; 0119-0125. Control unit 55 also calculates the true current plasma collection amount

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(Z), which is the volume of pure plasma collected. EX1004, ¶0119. Both are calculated each time the plasma collection bag 25's weight increases by 1 gram. EX1004, ¶0119.

75. True current plasma collection amount (Z) is calculated using Equation (V-3) below, which adds the true plasma collection amount collected up through the previous cycle (Y) (mL) to the apparent plasma collection amount collected since the start of that cycle (W) (mL), after subtracting anticoagulant admixture amount (X) (mL) from (W).

Equation (V-3): $$Z = Y + (W - X)$$

EX1004, ¶0126-127.

76. Anticoagulant admixture amount (X) is a volume of anticoagulant collected in the plasma collection bag 25 for a particular cycle of a procedure. See id. (X) is determined using equation V-2 in Takagi, shown below:

$$X\,[1st\ Cycle] = 0.0003W^2 + 0.3\,W + 0.4$$

$$X\,[2nd\ cycle\ and\ subsequent\ cycles] = 0.2\,W$$

EX1004, ¶0125.

77. Takagi thus calculates an anticoagulant volume in the plasma collection container as the plasma component is being collected by calculating (X) each time the plasma collection bag 25's weight increases by 1 gram. EX1004, ¶¶0119-125.

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

78. Takagi anticipates and/or renders obvious element 1[i] under any meaning of the term "based on." The claim language itself—"based, at least in part, on"—suggests that the calculation may rely on one or more methods and is not limited to a single, exclusive method. Although the '652 patent provides an example where a technician determines the volume of collected pure plasma by calculating the volume of anticoagulant in the plasma component—specifically, by measuring the volume of anticoagulant in the container and subtracting it from the total fluid volume in the collection container—the patent does not expressly disavow other reasonable interpretations of "based, at least in part, on." As explained below, Takagi anticipates and/or renders obvious this limitation under both the plain and ordinary and narrower meanings of "based, at least in part, on."

79. Takagi calculates true current plasma collection amount (Z) (the volume of pure plasma collected), each time plasma collection bag 25's weight increases by 1 gram. EX1004, ¶0119. To determine (Z),control unit 55 uses Equation (V-3) below, which adds true plasma collection amount (Y) collected through the previous cycle to apparent plasma collection amount (W) (mL) collected since the

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start of the current cycle, after subtracting anticoagulant admixture amount (X) (mL) from (W).:

Equation (V-3): $Z = Y + (W - X)$

EX1004, ¶0126-127. The true current plasma collection amount (Z) is displayed in real time during a procedure on display means 4. EX1004, ¶0128.

80. Anticoagulant admixture amount (X) is a volume of anticoagulant collected in plasma collection bag 25 during a cycle, determined using equation V-2, which relies on a predetermined ratio of anticoagulant to incoming whole blood. See §IX.A.9.; EX1004, ¶0125.

$$X\,[1st\ Cycle] = 0.0003W^2 + 0.3\,W + 0.4$$

$$X\,[2nd\ cycle\ and\ subsequent\ cycles] = 0.2\,W$$

Thus, for each cycle, the calculation of true current plasma collection amount (Z) is based at least in part on a calculated volume of anticoagulant in the collected plasma component (i.e. (X)).

81. Takagi's collection procedure may include multiple cycles, the number of which is determined based on the target collection amount of plasma. EX1004, ¶¶0011, 0068, 0131. In each cycle, (Z) is calculated by subtracting (X) from (W), and adding the result to (Y), where (Y) is a summation of the (Z) calculations for the previous cycles. Thus, a POSITA would understand that Takagi discloses a system

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that calculates the total volume of pure plasma collected within the plasma collection container (i.e., (Z) after the final collection cycle) based, at least in part, on a calculated volume of anticoagulant in the collected plasma component due to the inclusion of anticoagulant admixture amount (X) in each cycle of Takagi's collection procedure.

k. 1[j] continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container.

82. As discussed above, Takagi performs steps (d) – (i). See §§X.A.1.e-j.

83. In a procedure with Takagi's blood component collection device 1, the true current plasma collection amount (Z) (ml), or volume of pure plasma collected, is calculated each time the weight of plasma collection bag 25 increases by 1 gram during a procedure. EX1004, ¶0119. Control unit 55 determines whether the plasma collection operation has been completed based on (i) whether the true current plasma collection amount (Z) has reached M% of the true target plasma collection amount (D), or (ii) whether the plasma collection operation has been performed over a certain number of cycles (E). EX1004, ¶0131. Takagi discloses that "more preferably" (M) is "80 to 100%." EX1004, ¶0132. When M% of the true target plasma collection amount (D) is 100%, Takagi teaches continuing steps (d) through

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(i) until the target volume of pure plasma is collected within the plasma collection container.

2. Claim 5: A method according to claim 1, further comprising: monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection container based, at least in part, on the monitored volume of collected plasma component.

84. Takagi monitors a volume of plasma component (e.g., apparent plasma collection amount (W) (mL)) collected within the plasma collection container and uses (W) to calculate a volume of pure plasma (e.g., the true current plasma collection amount (Z) (ml)) in the plasma component. See §§X.A.1.i-j.; EX1004, ¶0126-127. EX1004, ¶0126-127. As discussed above in §§X.A.1.i-j., Takagi updates (W) as the system withdraws blood.

85. In Takagi, (W) is determined by the weight of the plasma collection bag 25. EX1004, ¶0119-125. Specifically, Takagi uses current apparent plasma weight (U), in grams, and apparent plasma weight (V) collected up through the previous cycle to determine collection volume (W) using Equation V-1:

$$W = (U - V)/1.03$$

EX1004, ¶0120-122.

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86. Therefore, the volume of pure plasma collected within the plasma collection container is based, at least in part, on the monitored volume of the collected plasma component.

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

87. *See* §X.A.2. Takagi monitors a weight of plasma component (e.g., current apparent plasma weight (U)) collected within the plasma collection container. EX1004, ¶0120-122. Takagi discloses that the current total volume of pure plasma in the collection container (true current plasma collection amount (Z)) is based on the apparent plasma collection amount (W), or "the monitored volume of collected plasma component," which is based on the weight of the collected plasma component (e.g., the current apparent plasma weight (U)). EX1004, ¶¶0120-122, 0126-127.

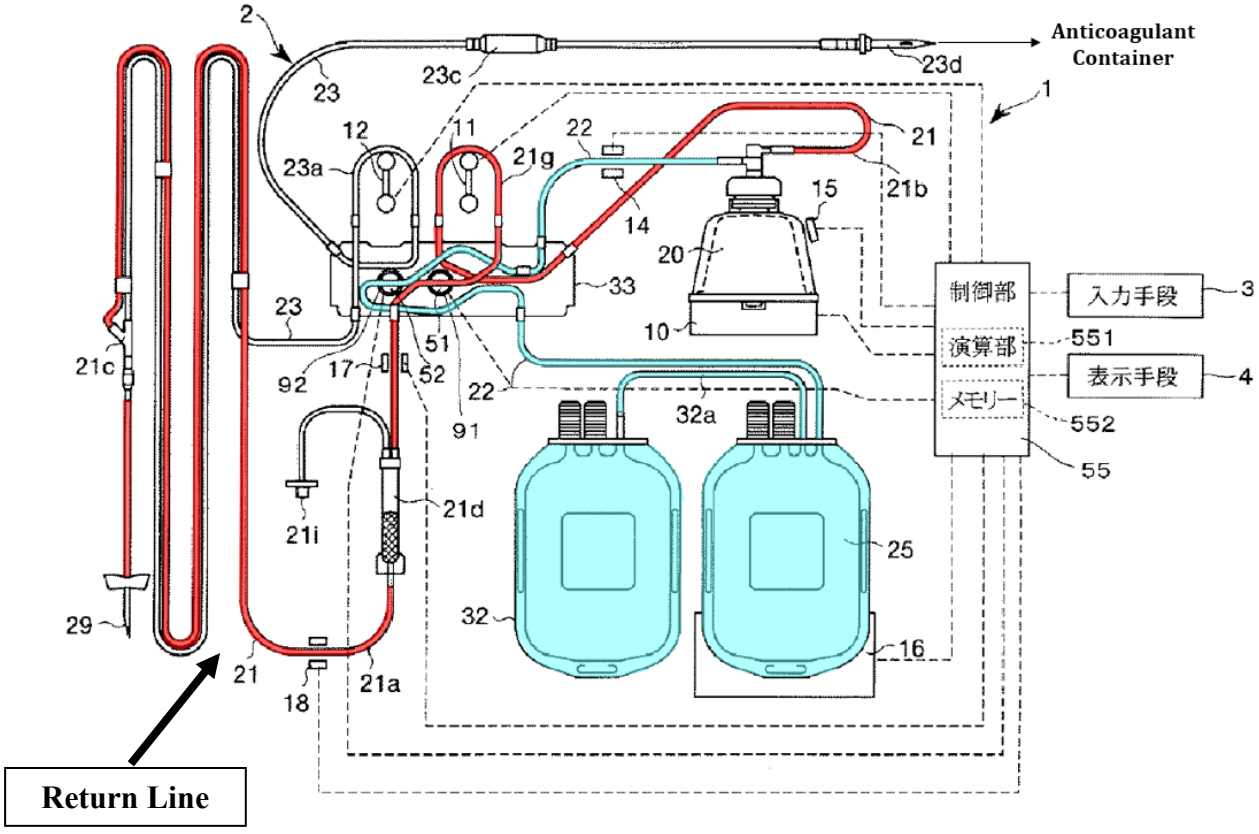
4. Claim 8: A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

88. Takagi discloses, "[t]he computing unit 551 in the control unit 55 may [ ] determine the true target plasma collection amount D [mL] based on donor information (gender, weight, and height) using Equation (II-0)." EX1004, ¶0089.

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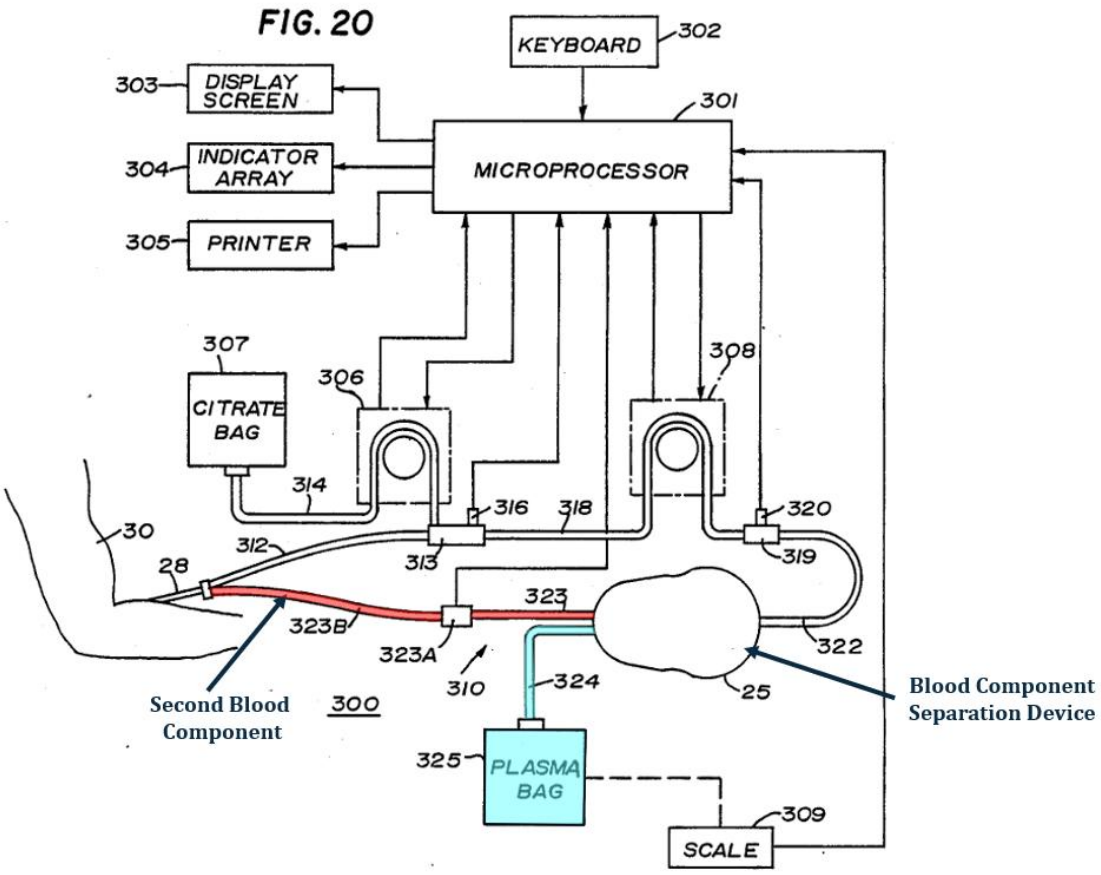
5. Claim 10: A method according to claim 1, further comprising returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line.

89. Takagi collects a first blood component (e.g., plasma), and a second blood component (e.g., any non-plasma blood component), is returned to the donor. EX1004, ¶¶0021, 0065-0066, 0139. Takagi discloses a single draw and return line, specifically first line 21 shown in Figure 1, however, if the Board finds that a separate return line is required, a POSITA would readily understand that a separate return line could be used instead of the single draw and return line (e.g. first line 21), as was well known in the art at the time of the '652 patent. EX1004, ¶¶0021, 0065.



EX1004, FIG. 1 (annotated).

90. Lavender provides an example of a blood separation system that includes separate draw and return lines, which was readily known in the art at the time of the effective filing date of the '652 patent. Specifically, Lavender collects a first blood component (e.g., plasma) in a "blood fraction collection receptacle or bag." EX1005, 5:32-33. The second blood component (e.g., RBC), is returned to donor 30 through tubing 323. EX1005, 10:58-63.



EX1005, FIG. 20 (annotated).

6. Claim 11

a. 11[preamble] A system for collecting plasma comprising:

91. Takagi discloses that its methods may be implemented in "a system for harvesting plasma." EX1004, ¶¶0003, 0070.

b. 11[a] a venous-access device for drawing whole blood from a subject and returning blood components to the subject;

92. *See* §§ X.A.1.d and X.A.5, supra, EX1004, ¶¶0023, 0061, 0071.

bb. 11[aa] a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container;

93. *See* §§ X.A.1.e, X.A.1.g, and X.A.1.h.

c. 11[b] a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump;

94. *See* §X.A.1.e., supra, EX1004, ¶0024.

d. 11[c] an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

95. *See* §X.A.1.f., supra, EX1004, ¶0021.

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e. 11[d] a controller configured to control the operation of the blood component separation device and the blood draw pump,

96. *See* §X.A.1.g., supra, EX1004, ¶0021. Takagi recites:

The control unit 55 controls the operations of the blood component collecting device 1, that is, the rotation, stopping, or rotation direction (forward/reverse) of the fluid supplying pumps 11, 12, . . . and the operation of the centrifuge drive unit 10 as needed.

See EX1004, ¶0062.

f. 11[e] the controller configured to calculate (1) a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma container,

97. *See* §X.A.1.h., supra, EX1004 ¶0119-127.

g. 11[f] (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the volume of anticoagulant in the collected plasma component,

98. *See* §§X.A.1.i. and X.A.1.j., supra, EX1004 ¶0119-127.

h. 11[g] the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

99. *See* §X.A.1.k, supra. EX1004, ¶¶0119, 0131.

7. Claim 16: A system according to claim 11, a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the

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plasma component based, at least in part, on the monitored volume of collected plasma component.

100. *See* §X.A.2.

8. Claim 17: A system according to claim 11, a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma component based, at least in part, on the monitored weight of collected plasma component.

101. *See* §IX.A.3.

9. Claim 19: A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the subject.

102. *See* §IX.A.4.

B. Ground 2: Claims 1, 3, 5, 6, 8, 10-12, 14, 16-17, and 19 are anticipated or rendered obvious by Lavender

1. Claim 1

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

103. To the extent the preamble is limiting, Lavender discloses "[a] system, method and device for continuously fractionating blood in situ." EX1005, Abstract. Lavender fractions blood "to collect blood substances, such as plasma." EX1005, 1:12-13; see also id. at claim 1 ("A method of collecting plasma…."), 5:42-49, 1:48-56.

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

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104. Lavender determines a weight of a donor through "entry and validation of donor data, including ... donor weight in pounds." EX1005, 20:10-14; see also EX1005 Abstract.

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

105. Lavender determines a hematocrit of a donor through "entry and validation of donor data, including … donor hematocrit in percent." EX1005, 20:10-14.

d. 1[c] inserting a venous-access device into the donor;

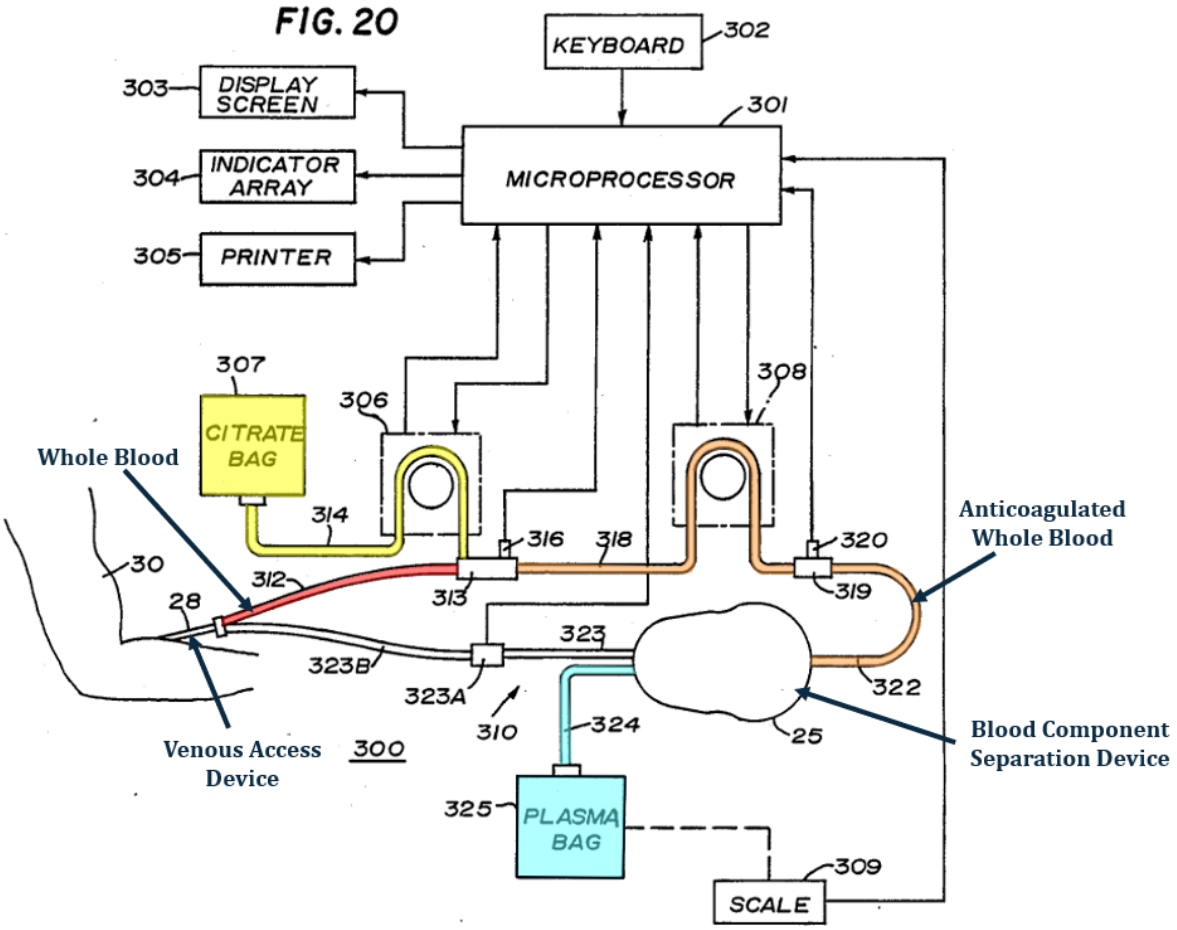
106. Lavender's blood fractionator uses a catheter, needle, or double lumen needle inserted into an appropriate vein or artery of the donor to draw blood from the donor for processing, allowing blood to flow from the catheter or needle through a blood tube and into an inlet of the blood fractionator. EX1005, 5:13-22, FIGS. 1, 20.

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

107. Lavender withdraws whole blood through the venous-access device. A pump "pump[s] blood from the donor" through the needle 28, through the tubes 312,

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318, 322 and into the fractionator 25, shown below in FIG. 20. EX1005, 5:18-22, Fig. 20.



EX1005, FIG. 20 (annotated).

The drawn blood is whole blood because it is a mixture of "a variety of blood fractions." EX1005, 5:45.

108. The draw line is connected to blood fractionator 25, as "[t]he blood fractionator has an inlet …, the inlet being connected to the donor by a blood tube." EX1005, 5:13-16, Figs. 1 & 20.

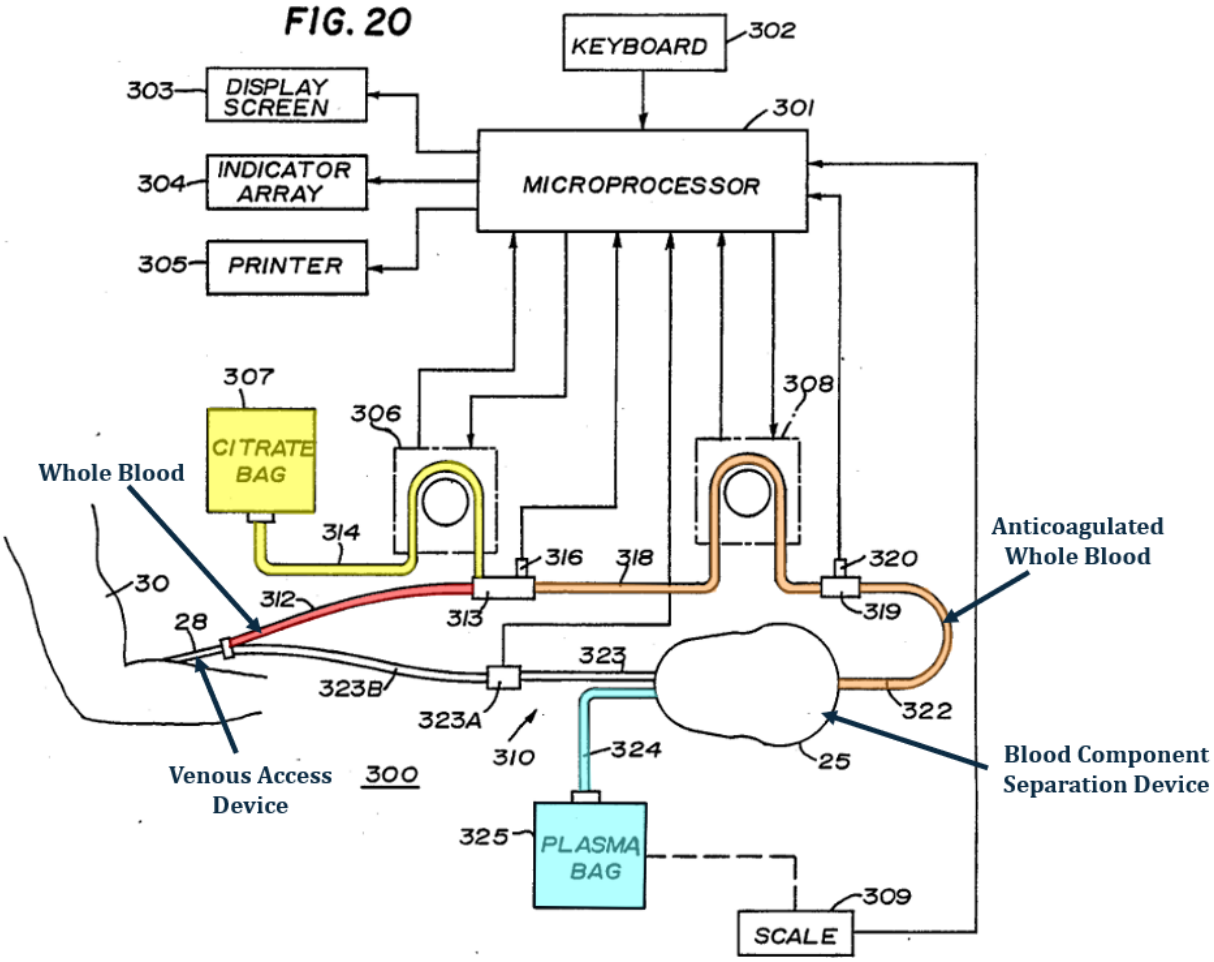
109. Blood fractionator 25 is a blood component separation device because "it produces a variety of blood fractions" from whole blood, "plasma [being] one of the most important blood fractions." EX1005, 5:42-45.

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

110. In Lavender's automated system for separating blood into components, "[a] supply of anticoagulant 35 is connected to the tube 27" supplying withdrawn whole blood from the donor. EX1005, 5:22-28, FIGS. 1, 20. "[A] second pump 31A …provide[s] a predetermined flow rate … of anticoagulant with the blood flowing

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from the donor 30 to the fractionator" via an anticoagulant line 314. EX1005, 5:22-28 and FIGS. 1, 20 (tube 314). EX1005, FIG. 20 (annotated).



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

111. The whole blood drawn from the donor flows into Lavender's blood fractionator 25, which separates it into blood fractions (components), including a

plasma component and a component containing red blood cells, white blood cells, and platelets. EX1005, 1:21-25, 5:42-52, 10:58-11:6, Figs. 1 and 20.

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

112. Lavender discloses that after the blood components are separated within the fractionator, "a plasma outlet port … allows plasma to flow to a plasma collection bag" via tubing (e.g., tubing 324 in Fig. 20). EX1005, 10:58-11:6; Figs. 1, 4, 15, 17, and 20.

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

113. Lavender calculates a volume of anticoagulant collected in the collected plasma component as the plasma component is being collected in the plasma collection container. Lavender weighs the collected plasma and anticoagulant solution in plasma bag 325 and transmits the weight information to microprocessor 301. EX1005, 16:50-53; 17:14-16. Using the total weight in the plasma bag, system 300 calculates the volume of anticoagulant in the plasma bag 325 (i.e. total citrate filtered (***TCF***)) by multiplying the total amount of filtered plasma (***TPF***) by a

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conversion factor (CF)[3] for milliliters of citrate per milliliter of plasma. EX1005, 41:1-44:33 (Table VI, §5(B)). CF is determined using a predefined ratio of citrate added per milliliter of plasma to dilute incoming plasma to 68% of the initial concentration. EX1005, 22:35-46.

114. Lavender's microprocessor repeatedly measures the weight change of the plasma bag ("$TDPW$", total dilute plasma filtered in grams) in real time and updates the calculated values using the updated total weight in the plasma bag. EX1005, 20:55-68; 41:1-44:33. Specifically, Lavender discloses "repeatedly performing the measurements and calculations . . . updating these values each time the program cycles through the main loop, and displaying the values in 'Run'-message (Table V) which is updated approximately every two seconds." EX1005, 20:55-68; 41:1-44:33.

[3] I note that Table VI has two different "CF" terms, (i) conversion factor (CF) and (ii) the rate citrate is pumped into the donor's whole blood, or citrate filtered in ml/min (CF). This appears to be a typographical error and a POSITA would understand that "CF" used in the total citrate filtered (TCF) equation is conversion factor (CF).

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115. Lavender thus calculates the anticoagulant volume as the plasma component is being collected in the plasma collection container by repeatedly performing the TCF calculation in the main loop of the algorithm in real-time, which continues until the total plasma filtered is equal to or greater than the maximum total plasma filtered. EX1005, cols. 43-44.

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

116. Lavender anticipates element 1[i] under the plain and ordinary meaning of the term "based on" discussed above in §X.A.1.i. Alternatively, as discussed below, a POSITA would have understood that Lavender renders this limitation obvious under the plain and ordinary meaning.

117. Lavender uses the amount of anticoagulant (citrate) added to the whole blood to calculate the total pure plasma volume collected. EX1005, 20:55-68; 41:1-44:33. Lavender first calculates total plasma filtered ($\boldsymbol{TPF}$), representing the total amount of pure plasma in the plasma collection bag. EX1005, 20:55-68; 41:1-44:33. TPF is determined by multiplying the total amount of dilute plasma filtered ($TDPF$) by a plasma dilution factor (PDF) (i.e., $\boldsymbol{TPF} = TDPF * PDF$). EX1005, 20:55-68; 41:1-44:33. PDF is determined using the predefined ratio of citrate added per milliliter of plasma to dilute incoming plasma to 68% of the initial concentration.

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EX1005, 22:35-46. Thus, 32 ml of citrate is added to the incoming whole blood for every 68 ml of plasma to dilute the incoming plasma to 68% of its initial concentration; and PDF is defined at .68. EX1005, 20: 35-46; 41:1-44:33.

118. Next, Lavender calculates the anticoagulant volume in the plasma container (i.e. total citrate filtered (***TCF***)). See §X.B.1.i.

119. As shown in the annotated excerpt of §5(B) of Table VI below, the volume of pure plasma in the plasma collection bag (***TPF***) and the volume of anticoagulant in the plasma container (***TCF***) share a direct mathematical relationship.

```
TPF=TDPF*PDF        (total plasma filtered, ml)
CF=PF*CF            (citrate filtered, ml/min)
TCF=TPF*CF          (total citrate filtered, ml/min)
```

120. That is, during collection, any change in the calculated value of the volume of anticoagulant (***TCF***) requires a corresponding change in the calculated value of the volume of pure plasma (***TPF***), and vice versa. Both *TCF* and *TPF* are based on the predefined ratio of citrate added per milliliter of plasma to dilute incoming plasma to 68% of the initial concentration. EX1005, 22:35-46. Accordingly, the volume of pure plasma collected in the plasma collection bag (***TPF***) is calculated in real-time based "at least in part" on the calculated volume of

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anticoagulant in the collected plasma component (***TCF***) because both TPF and TCF are dependent on the predefined ratio of citrate added per milliliter of plasma to dilute incoming plasma to 68% of the initial concentration and as one value changes, the other necessarily changes.

121. Lavender's disclosure of the dependency of both ***TPF*** and ***TCF*** on the predefined ratio of citrate added per milliliter of plasma inherently discloses calculating a volume of pure plasma collected in the plasma collection bag (***TPF***) based, at least in part, on a calculated volume of anticoagulant in the collected plasma component (***TCF***). If the Board, however, determines this is not inherent in Lavender, Lavender renders this limitation obvious because a POSITA would (i) recognize the interdependency between the predefined ratio of citrate added per milliliter of whole blood, TPF and TCF, and (ii) understand that the plasma volume in the collection bag is based, at least in part, on the volume of anticoagulant in the collection bag.

k. 1[j] continuing steps (d) through (i) until a target volume of pure plasma is collected within the plasma collection container.

122. As discussed above, Lavender performs steps (d) – (i). See §§X.B.1.e-j.

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123. In response to the start of a blood separation procedure using Lavender's automatic system, the system initializes the system algorithm of Table VI. EX1005, 20:55-68, 41:1-44:33, Figs. 25A-25D. The Main Loop of the algorithm repeats until a desired amount of plasma has been collected. EX1005, 21:62-22:2.

124. For example, Lavender repeats step (d)-(i) by "introducing anticoagulant to the blood from which the plasma is to be collected … separating plasma from the extracted blood … until a predetermined … volume of plasma has been collected." 4 EX1005, 21:62-22:6; 46:14-22; see also claim 1.

2. Claim 3: A method according to claim 1, further comprising: determining a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the number of rotations of the anticoagulant pump.

125. Lavender determines a volume of anticoagulant introduced into the whole blood based on a number of rotations of an anticoagulant pump. EX1005, 41:27-30; 42:8-44:32. Lavender uses anticoagulant pump 306 in system 300 "for pumping anticoagulant from an associated source" into "the blood flowing from the donor 30 to the fractionator 25." EX1005, 5:15:47-53, 16:45-47, 16:54-17:2, claim 1; Fig. 20. Lavender introduces anticoagulant into the whole blood at "a

[4] All emphasis added unless otherwise noted.

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predetermined flow rate," which Lavender expresses in its algorithm as QC. EX1005, 5:25-26. Lavender sets the citrate pump flow rate, QCP, to QC. EX1005, cols. 41 & 42.

126. Lavender also calculates the volume of anticoagulant in the collected plasma component based on the number of rotations of the anticoagulant pump. Lavender discloses that "[t]he flow rate of the anti-coagulant and the blood are fixed by the pumps 31 and 31A used in conjunction with the supply 35 of anti-coagulant." 15:47-53. Further, as shown in §2 of Table VI, the rotations of citrate pump (***CRPM***) and blood pump (***BRPM***) are calculated based on the citrate pump flow rate (***QCP***) and blood pump flow rate (***QBP***). See Table VI, §2.

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

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

$$= QB + QP * CF$$

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

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

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based, at least in part, on the number of rotations of the anticoagulant pump (citrate pump $\boldsymbol{CRPM}$). For example,

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

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

$$= CRPM * \frac{CMR}{[(BRPM*BMR-CRPM*CMR)*(1-HCTD)]}$$

and $PDF = \frac{1}{CF+1}$.

3. Claim 5: A method according to claim 1, further comprising: monitoring a volume of plasma component collected within the plasma collection container, the calculated volume of pure plasma collected within the plasma collection container based, at least in part, on the monitored volume of collected plasma component.

128. Lavender monitors a volume of plasma component (e.g., TDPF total dilute plasma filtered) collected within the plasma collection container. EX1005, 43:4-6. As discussed above in §X.B.1.j., Lavender updates TDPF as the system withdraws blood.

129. Lavender uses the monitored volume of collected plasma component (e.g., TDPF) to calculate a volume of pure plasma (e.g., TPF total plasma filtered) in the plasma component (e.g., TPF is the product of TDPF and PDF, the plasma dilution factor). EX1005, 41:1-44:40. Therefore, the volume of pure plasma

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collected within the plasma collection container is based, at least in part, on the monitored volume of the collected plasma component.

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

130. Lavender monitors a weight of plasma component (e.g., TDPW total weight of dilute plasma filtered) collected within the plasma collection container. See Table VI, §5(B). Lavender discloses that the current total volume of pure plasma in the collection container (TPF) is based on the TDPF, or "the monitored volume of collected plasma component," which is based on the weight of the collected plasma component (TDPW). EX1005, 41:1-44:33.

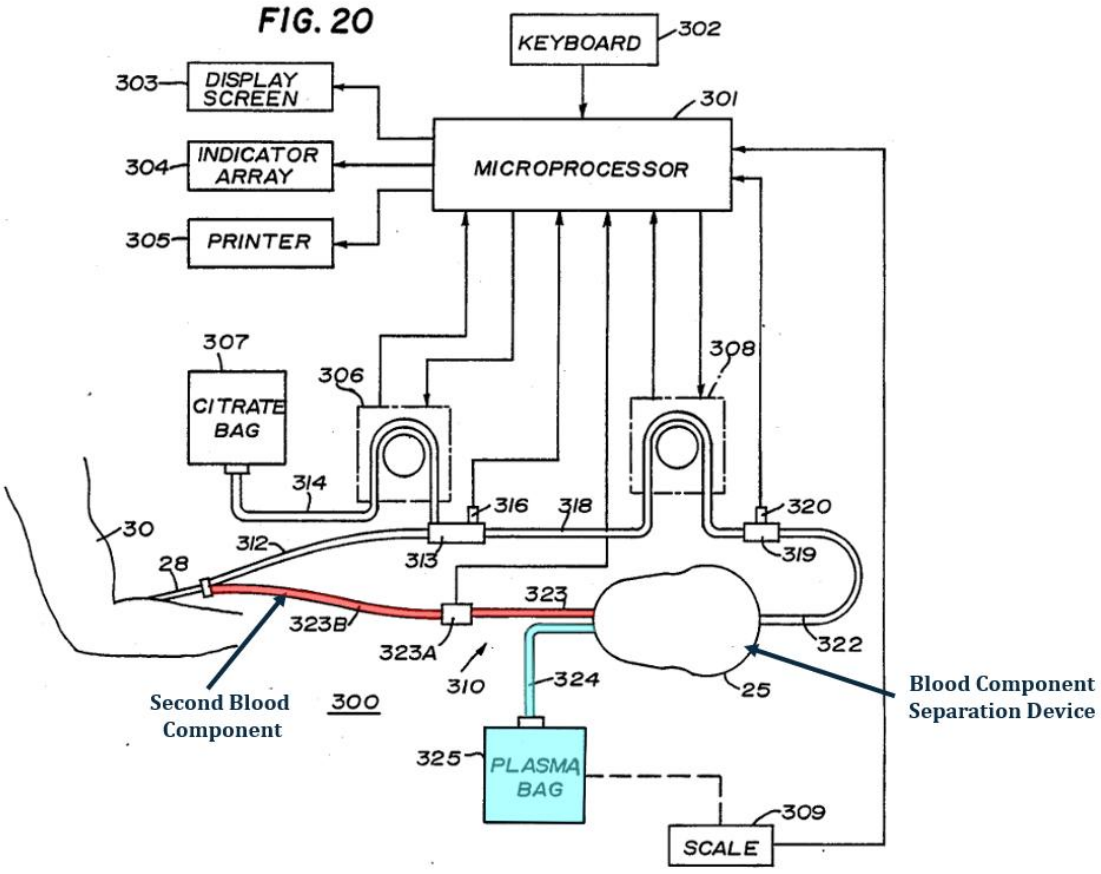
5. Claim 8: A method according to claim 1, wherein the target volume of pure plasma is based, at least in part, on the weight of the donor.

131. Lavender discloses directing "the user in entry and validation of donor data, including … donor weight in pounds." EX1005, 20:10-14. Then, Lavender determines a target volume of pure plasma, $\boldsymbol{MAXPF}$, which is based on the donor's bodyweight ($\boldsymbol{BW}$) and a predetermined constant ($C1$) of milliliters of plasma collected per pound of body weight. EX1005, Table VI, §2(g).

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6. Claim 10: A method according to claim 1, further comprising returning, after collecting at least a portion of the target volume of pure plasma, the second blood component to the donor through a return line.

132. Lavender collects a first blood component (e.g., plasma) in a "blood fraction collection receptacle or bag." EX1005, 5:32-33. The second blood component (e.g., RBC), is returned to donor 30 through tubing 323. EX1005, 10:58-63.



EX1005, FIG. 20 (annotated).

7. Claim 11

a. 11[preamble] A system for collecting plasma comprising:

133. Lavender discloses that its methods may be implemented in "a system for harvesting plasma." EX1005, Abstract, 1:15-17, 1:45-47, Figs. 1 & 20.

b. 11[a] a venous-access device for drawing whole blood from a subject and returning blood components to the subject;

134. *See* §§X.B.1.d and X.B.6, supra, EX1005, 5:13-22 and Figs 1 and 20.

bb. 11[aa] a blood component separation device for separating the drawn blood into a plasma component and a second blood component, the blood component separation device having an outlet and being configured to send the plasma component to a plasma container;

135. *See* §§ X.B.1.e, X.B.1.g, and X.B.1.h.

c. 11[b] a blood draw line fluidly connected to the venous-access device and configured to transport drawn whole blood to the blood component separation device, the flow through the blood draw line being controlled by a blood draw pump;

136. *See* §X.B.1.e, supra, EX1005, 5:13-22 and Figs 1 and 20.

d. 11[c] an anticoagulant line connected to an anticoagulant source, the anticoagulant line configured to introduce anticoagulant into the drawn whole blood; and

137. *See* §X.B.1.f, supra, EX1005, 5:22-28 and Figs. 1 and 20.

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e. 11[d] a controller configured to control the operation of the blood component separation device and the blood draw pump,

138. *See* §X.B.1.g, supra, EX1005, 10:58-11:6; and Figs. 1 and 20. Lavender recites:

> The input and output pressures of the blood pump are sensed and inputted to a microprocessor, into which donor data including weight, sex, and hematocrit is also keyed by the user. The microprocessor operates under program control to calculate, based on the donor data, the amount of plasma to be collected and the amount of anticoagulant to be added. The program controls the operation of the extracorporeal devices, regulates the operating parameters, and stops the procedure when the predetermined amount of plasma has been obtained."

See EX1005, Abstract. This program control of the extracorporeal devices includes the fractionator (blood component separation device) and associated fluid pumps. EX1005, 18:27-64; claims 28, 29, 33, 35, 36, 38, and 40-41.

f. 11[e] the controller configured to calculate (1) a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma container,

139. *See* §X.B.1.i, *supra,* EX1005, 10:58-11:6; and Figs. 1 and 20.

140. Lavender's microprocessor 301 executes the Main Loop algorithm of Table VI while the automatic system 300 is drawing blood from the donor for separation and calculates the total citrate filtered (TCF) collected in the plasma bag 325. EX1005, 20:55-68; 41:1-44:33. Thus, the automatic system 300 includes "a

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controller configured to (1) calculate a volume of anticoagulant in the collected plasma component as the plasma component is being collected in the plasma collection container."

g. 11[f] (2) a volume of pure plasma collected within the plasma container based, at least in part, upon the volume of anticoagulant in the collected plasma component,

141. *See* §X.B.1.j, *supra,* EX1005, 8:29-64; 20:55-68; EX1005, 22:35-39; 41:1-44:33. Petitioner notes that system 300's microprocessor 301 executes the algorithms detailed in Table VI of Lavender. EX1005, 18:53-56.

h. 11[g] the controller configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container.

142. Lavender's controller is configured to stop the blood draw pump when a target volume of pure plasma is collected within the plasma container. *See* §X.B.1.k, *supra*. EX1005, 21:l-22:6; §5(C) of Table VI.

8. Claim 12: A system according to claim 11, wherein the volume of anticoagulant in the collected plasma component is based, at least in part, on a volume of anticoagulant added to the drawn whole blood and the subject's hematocrit.

143. Lavender discloses claim 12 under the plain and ordinary meaning of the term "based, at least in part, upon." The claim language itself—"based, at least in part, upon"—suggests that the calculation may rely on interrelated methods and

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not just a single, exclusive approach. While the '652 patent provides an equation for calculating the percentage of anticoagulant in the collected plasma (AC %) based on the donor's hematocrit, it does not specify how the volume of anticoagulant in the collected plasma is calculated. The specification states that "[o]nce the technician/system 100 has calculated the percentage of anticoagulant within the plasma collection container 216 … the technician/system 100 may determine the volume of anticoagulant within the container (based on the percentage of anticoagulant within the container 216)." EX1001, 8:47-54. As explained below, Lavender anticipates this claim under the plain and ordinary meaning of "based, at least in part, upon." Alternatively, as discussed below, a POSITA would have understood that Lavender renders this claim obvious.

144. In Lavender's automatic system 300, the user enters donor data, including hematocrit, weight, and sex, before initializing the system algorithm. EX1005, 20:10-14, 55-67. The algorithms shown in Table VI use donor data, including hematocrit (***HCTD***), to calculate various interrelated equations. EX1005, 41:1-44:42 (Table VI). These equations determine collection volumes like the citrate (anticoagulant) volume (***TCF***) and the pure plasma volume (***TPF***). EX1005, 41:1-44:42 (Table VI).

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

146. For example, ***TCF*** and ***TPF*** are both calculated based on the total volume of collected dilute plasma (***TDPF***), which is converted from the total dilute plasma filtered weight (***TDPW***), which is the measured total weight of the dilute plasma collected based on the amount of total plasma flow (***TQP***). ***TQP*** is a donor specific amount based on hematocrit (***HCTD***) that determines how much anticoagulant needs to be added to dilute the donor's blood to 68% of the original plasma concentration, which, in turn, changes ***TDPW*** and ***TDPF***. EX1005, 41:4-44:42; EX1005, 22:35-43. Thus, any change in the donor's hematocrit value (***HCTD***) requires a corresponding change in the calculated value of the volume of anticoagulant (***TCF***), and vice versa so the volume of anticoagulant collected in the plasma collection bag (***TCF***) is calculated based, at least in part, on the donor's hematocrit (***HCTD***).

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147. A POSITA would understand that Lavender also directly calculates the volume of anticoagulant in plasma bag 325 based, at least in part, upon the hematocrit of the donor. System 300 uses the plasma bag 3 weight to calculate the volume of anticoagulant in plasma bag 325 (i.e., total citrate filtered (***TCF***)) by multiplying a volume of the total amount of filtered plasma (***TPF***) by conversion factor (CF) (expressed as $TCF = TPF * CF$), where ***CF*** represents the volume of anticoagulant introduced into the incoming whole blood ($\boldsymbol{V_{AC}}$) per incoming volume of plasma ($\boldsymbol{V_P}$), or $CF = \frac{V_{AC}}{V_P}$.. EX1005, 41:1-44:42 (Table VI, §5(B)). Conversion factor (CF) is determined using a predefined ratio of citrate added per milliliter of whole blood to dilute incoming plasma to 68% of the initial concentration. EX1005, 22:35-46.

148. Lavender weighs the collected plasma and anticoagulant solution in plasma bag 325 and transmits the weight to microprocessor 301. EX1005, 16:50-53; 17:14-16. Total plasma in the collected plasma component (***TPF***) is calculated based on the total volume of anticoagulant and plasma mixture in the collection container (total dilute plasma filtered (***TDPF***)), which is determined using the collection container's weight. The ***TPF*** equation is $TPF = TDPF * PDF$. Plasma dilution factor (***PDF***) represents the ratio of incoming plasma volume (V_P) to the sum of incoming plasma volume and anticoagulant volume (V_{AC}). EX1005, 22:37-39;

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41:10-44:57. A POSITA would understand this would be expressed as: $PDF = \frac{V_P}{V_P+V_{AC}}$.

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

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

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

150. Lavender therefore determines the volume of anticoagulant in the collected plasma from $TCF = \frac{TDPF*V_{AC}}{[V_{AC}+V_B*(1-HCTD)]}$, showing that Lavender determines the volume of anticoagulant in the collected plasma from the volume of anticoagulant added to the whole blood and the subject's hematocrit. Therefore, Lavender renders this limitation obvious because a POSITA would understand that Lavender's volume of anticoagulant is directly calculated based on the donor's hematocrit.

9. Claim 14: A system according to claim 11, wherein the controller is configured to monitor a number of rotations of an anticoagulant pump to determine a volume of anticoagulant introduced into the whole blood, the

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calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the number of rotations of the anticoagulant pump.

151. *See* §X.B.2.

10. Claim 16: A system according to claim 11, a plasma container weight sensor configured to monitor a volume of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma component based, at least in part, on the monitored volume of collected plasma component.

152. *See* §X.B.3.

11. Claim 17: A system according to claim 11, a plasma container weight sensor configured to monitor a weight of plasma component collected within the plasma container, the calculated volume of pure plasma collected within the plasma component based, at least in part, on the monitored weight of collected plasma component.

153. *See* §X.B.4.

12. Claim 19: A system according to claim 11, wherein the target volume of pure plasma is based, at least in part, on the weight of the subject.

154. *See* §X.B.5.

C. Ground 3: Claims 2, 9, 13, and 20 are obvious over Takagi in view of Min

1. Reasons to Combine Takagi and Min

155. A POSITA would have been motivated to combine Takagi's teachings with Min's and would have had a reasonable expectation of success in doing so. EX1006, 11:52-55, 17:17-22.

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156. Specifically, a POSITA would have been motivated to combine Takagi with Min's teachings of using weigh sensors 246 to track weight changes and derive fluid processing volumes, including volume changes of anticoagulant container 276 and plasma collection container 304. EX1006, 11:52-55, 17:17-22.

157. Additionally, a POSITA would found it obvious and would have had a reasonable expectation of success in modifying Takagi's blood component collection device 1 in view of Min because 1) each relate to the same well-known technologies, 2) both apply substantially similar techniques to achieve similar results, and 3) the functionality of Takagi would not change because Takagi is used for the same purpose as Min's system—monitoring the weight of an anticoagulant bag in an apheresis procedure to determine a change in volume within the anticoagulant container. EX1006, 11:52-55, 17:17-22.

158. Both Takagi and Min relate to the well-known technologies of separating blood components. Accordingly, a POSITA would have found it obvious to combine the teachings of Takagi with Min because they are in the same field of endeavor with the same well-known technologies. That is, combining Takagi and Min entails the use of known solutions to improve similar systems and methods in the same way, i.e., to use Min's technique of monitoring the weight of an

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anticoagulant bag to determine a volume of added anticoagulant to whole blood before separating blood components.

159. Takagi and Min also each apply substantially similar techniques to achieve similar results. As discussed above, Takagi discloses a blood component collecting device "that collects primarily plasma." EX1004, ¶0020. Similarly, Min discloses a system for "separating whole blood into plasma and red blood cells." EX1006, 4:26-29. A POSITA would have been motivated to add Min's monitoring of the weight (and volume) of an anticoagulant bag into Takagi's blood component collection device to provide another way of estimating the amount of anticoagulant in the plasma collection container.

160. Further, Min's disclosed systems for determining the amount of added anticoagulant functions substantially similarly to Takagi's technique of adding and monitoring the anticoagulant added to a blood separation system. Indeed, Min's anticoagulant container and tube arrangement (See Fig. 10) is structurally similar to Takagi's (See Fig. 1). EX1006, 3:26-29. Therefore, it would have been obvious, and a POSITA would have been motivated, to modify Takagi's blood fractioning system to incorporate Min's monitoring of the change in the weight of the anticoagulant container. Additionally, it would have been an obvious design choice to use Min's anticoagulant monitoring scale in Takagi's blood component collection device to

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improve the accuracy of determining pure plasma volume based on the added anticoagulant volume.

161. The intended functionality of Takagi's blood component collection device would not change when used for monitoring the anticoagulant weight like in Min's apheresis system. That is, a POSITA would have expected Takagi´s blood component collection device to successfully determine the amount of anticoagulant added to the system from the anticoagulant container.

162. Additionally, Takagi discloses converting a weight change to volume change using a specific gravity. EX1004, ¶121. Because Takagi uses a weight sensor to track the volume of the plasma collection bag, a POSITA would have had a reasonable expectation of success adding Min's weight sensor to monitor the anticoagulant bag. Accordingly, a POSITA would have understood that the weight of the anticoagulant bag, and corresponding volume could be implemented in Takagi's algorithms to determine the volume of anticoagulant in the collected plasma component. Further, a POSITA would have understood that calculating the added anticoagulant volume based on Min's weight sensors would reduce potential errors in determining the volume of anticoagulant.

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

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based, at least in part, on the change in volume within the anticoagulant container.

163. Takagi discloses a control unit that monitors the volume change in a collection container by converting a change in weight to a change in volume using specific gravity. §X.C.1. Min uses weigh sensors 246 to track weight changes of the anticoagulant container and derive fluid processing volumes, including the volume change of anticoagulant container 276 and plasma collection container 304. EX1006, 11:52-55, 17:17-22. Each of Min's weigh sensors "provide output reflecting weight changes over time" and "[t]his output is conveyed to [a] controller. . . [for] process[ing] the incremental weight changes to derive fluid processing volumes." EX1006, 17:17-22.

164. Thus, the combined system discloses an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source (i.e. the weigh sensors of Min), the controller further configured to monitor a change in volume within the anticoagulant source based on the measured weight of the anticoagulant source (i.e. the controller of Min). EX1006, 17:17-22.

165. A POSITA would understand, and the '652 patent acknowledges, that substantially all of the anticoagulant added to a centrifuge-based blood fractionating system would end up in the plasma collection container. See §VIII.A.; EX1001 at 8:18-23. Thus, substantially all of the anticoagulant added to Takagi's blood

component collecting device 1 would end up in the plasma collection bag. A POSITA would have implemented Min's use of weight sensors to determine anticoagulant volume changes in the anticoagulant bag in Takagi's system and have used the anticoagulant volume as measured by Min's weight sensor for anticoagulant admixture (*X*) (the volume of anticoagulant in the collected plasma container).

166. A POSITA would understand that calculations, similar to Takagi's method of determining the apparent plasma collection amount W collected since the start of the cycle from the apparent weight of the plasma collected U and the apparent plasma weight V collected up through the previous cycle calculated in Equation (V-1), would be used to determine the anticoagulant admixture amount (X) using Min's anticoagulant source weight sensors. Those calculations would determine the anticoagulant admixture amount X collected since the start of the cycle from the difference in the weight measured by Min's anticoagulant source weight sensor up through the previous cycle and the anticoagulant source weight sensor since the start of the cycle, divided by the specific gravity of the anticoagulant.

3. Claim 9: A method according to claim 1, wherein the volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

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167. The volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn whole blood. Takagi uses an anticoagulant pump, second fluid supplying pump 12, in blood component collection device 1 for pumping anticoagulant fluid into the donor's whole blood prior to separation of blood components. EX1004, ¶0024; Fig. 1. At least a portion of the anticoagulant introduced in the withdrawn whole blood is collected in the plasma collection bag because anticoagulant is pumped "at [a] predetermined ratio (addition ratio) inputted by the operator." EX1004, ¶0103.

168. The volume of anticoagulant in the collected plasma component also includes at least a portion of the anticoagulant added during a priming step. Takagi discloses a priming step, e.g., "the operator primes the third line 23 and the blood collection needle 29 with the anticoagulant, and then inserts the blood collection needle 29 into a blood vessel of the blood donor. This completes the preparations for plasma collection." EX1004, ¶0076. Min also discloses that during the priming step, "the anticoagulant pump PP4 conveys a predetermined volume of anticoagulant (e.g., 10g) into the in-process container 312" where plasma is collected. EX1006, 22:40-42. Thus, at least a portion of the volume of anticoagulant in the collected plasma component (e.g. the plasma bag 325) would include at least a portion of the anticoagulant added during the priming step described above.

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169. A POSITA would have been motivated to combine the teachings of Takagi with Min for the same reasons as discussed above. §X.C.1. In addition, a POSITA would have looked to Min to calculate the volume of anticoagulant added during the priming step in the total collection volume, to reduce any errors that may occur by not accounting for such a priming step in determining the anticoagulant volume in the plasma collection bag.

4. Claim 13: A system according to claim 11, an anticoagulant source weight sensor configured to measure the weight of the anticoagulant source, the controller further configured to monitor a change in volume within the anticoagulant source based on the measured weight of the anticoagulant source, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the change in volume within the anticoagulant source.

170. *See* §§X.C.1, 2.

5. Claim 20: A system according to claim 11, wherein the volume of anticoagulant in the collected plasma component includes at least a portion of the anticoagulant introduced into the withdrawn blood and at least a portion of a volume of anticoagulant added during a priming step.

171. *See* §X.C.3.

D. Ground 4: Claims 7 and 18 are obvious over Lavender in view of Takagi, Headley, and Barrett

1. Claim 7: A method according to claim 1, further comprising: wherein step (b) includes monitoring a volume of red blood cells collected within the blood component separation device, the determined hematocrit of the donor based, at least in part, on the monitored volume of red

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blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the donor.

172. Lavender teaches determining a volume of whole blood withdrawn from the donor in the Main Loop algorithm, which calculates the total blood flow (***TQB***) in ml while blood is drawn. EX1005, 43:7-16. The pump rates for the blood pump and the citrate pump in Lavender's system are determined based on the donor's hematocrit. EX1005, 41:21-26.

173. Headley relates to systems and methods for separating platelets and other blood components from blood. EX1009, Abstract. Headley teaches using an optical sensor array 97 in a blood separation system (e.g. a centrifuge) to determine red blood cell volume within the blood separation system. EX1009, 1:10-24; 4:48-64. It would have been obvious for a POSITA to include Headley's optical sensor(s) in Lavender's blood separation device to determine the volume of red blood cells collected from the donor and allow the red blood cells to be immediately returned to the donor during the separation procedure.

174. Should the Board determine that Headley's optical sensor(s) are only effective within a centrifuge-based blood separation system, a POSITA would be motivated to replace Lavender's membrane-based blood fractionator with Takagi's centrifuge 20. EX1005, 6:3-12;, 46:16-43. It was generally known in the art that a

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centrifuge-based blood separation device, as compared to a membrane-based blood separation device, provided a comparable treatment quality in a shorter time period. *See* EX1010, p. 135. A POSITA would have been motivated to combine Lavender's system with Takagi's centrifuge-based collection device to more efficiently separate plasma from a donor's blood and reduce the overall procedure time.

175. A POSITA would have been motivated to combine Lavender's and Takagi's teachings, and would have had a reasonable expectation of success, because 1) each relate to the same well-known technologies, 2) both apply substantially similar techniques to achieve similar results, and 3) Lavender's functionality would not change in the combination as Takagi's centrifuge-based blood component collection device is used for the same purpose as Lavender's system—using donor parameters to determine the total amount of pure plasma to collect and separating a donor's blood to collect pure plasma.

176. Barrett teaches determining a donor's hematocrit by dividing a blood sample's red blood cell volume over the total volume of the blood sample. EX1008, 2:45-49.

177. A POSITA would have been motivated to combine the teachings of Lavender, Takagi, and Headley with Barrett to determine a real-time hematocrit of a donor during a collection procedure. Each of Lavender, Takagi, Headley, and

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Barrett relate to the well-known technologies of separating blood components. Accordingly, a POSITA would have found it obvious to combine the teachings of Lavender, Takagi, Headley, and Barrett because they are in the same field of endeavor with the same well-known technologies.

178. Additionally, Lavender, Takagi, Headley, and Barrett, apply substantially similar techniques to achieve similar results. As discussed above, Lavender discloses fractionating blood "to collect blood substances, such as plasma." EX1005, 1:12-13. Barrett also teaches patient blood data acquisition and management for hemodialysis patients in preparation for blood separation procedures. EX1008, 1:6-19.

179. A POSITA would want to incorporate Barrett's teaching of determining a donor's hematocrit by dividing the total red blood cell volume of a blood sample over the total volume of a blood sample into Lavender's Main Loop algorithm to determine the donor's hematocrit as blood is being drawn from the donor. A POSITA would recognize this would reduce error in Lavender's calculated values and account for the change in the donor's hematocrit as blood is being drawn. For example, the pump rates of Lavender's system, which are determined based on hematocrit of the donor, may be more accurately regulated if hematocrit is updated in real time during a procedure. EX1005, 41:21-26.

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180. Thus, a POSITA would use both (i) the monitored volume of red blood cells collected during a blood separation procedure from Headley, and (ii) the volume of whole blood withdrawn from the donor, or total blood flow (TQB) in Lavender, to determine a donor's real-time hematocrit in Lavender's Main Loop algorithm. This equation could simply be added into the Main Loop algorithm of Lavender and would increase the accuracy of Lavender's calculated estimates. Also, to more effectively separate blood components in Lavender's system, a POSITA would be motivated to replace the membrane-based blood fractionator in Lavender with Takagi's centrifuge 20. §X.C.1 and 3; EX1005, 6:3-12; 46:16-43.

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

182. Accordingly, Lavender in view of Takagi, Headley, and Barrett teach monitoring a volume of red blood cells collected within the blood component

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separation device because Headley teaches monitoring the volume of collected red blood cells. EX1009, 1:10-24; 4:48-64; 17:19-24; EX1008, 2:45-49. The determined hematocrit of the donor based, at least in part, on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the donor is taught by Barret's equation for hematocrit, which determines hematocrit by dividing the red blood cell volume of a blood sample (e.g. the volume of red blood cells collected) by the total volume of the blood sample (e.g. total blood flow into the system, Lavender's TQB). EX1005, 41:8-44:32; EX1006, 12:22-25; 17:19-24; EX1009, 1:10-24; 2:45-49; 4:48-64.

2. Claim 18: A system according to claim 11, an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood component separation device, the controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the subject.

183. *See* §X.D.1. As discussed above, Headley teaches the use of an optical sensor array 97 in a blood separation system (e.g. a centrifuge to determine a red blood cell volume within the blood separation system. EX1009, 1:10-24; 4:48-64. Thus, Headley discloses an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the

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blood component separation device. See §X.D.1.; EX1009, 1:10-24; 4:48-64. It would be obvious for a POSITA to replace the optical sensor 15 in Takagi's blood separation device (e.g. centrifuge 20) with the optical sensor array 97 of Headley to determine a red blood cell volume within the centrifuge 20. EX1004, ¶0051.

184. Accordingly, Lavender in view of Takagi, Headley, and Barrett teaches an optical sensor located on the blood component separation device and configured to monitor a volume of red blood cells collected within the blood component separation device using Headley's optical sensor. EX1009, 4:48-64. Using Lavender's Main Loop algorithm and Barrett's equation to determine hematocrit, Lavender, modified in view of Takagi, Min, Barrett, and Headley teaches a controller configured to determine the subject's hematocrit based, at least in part, upon on the monitored volume of red blood cells collected within the blood component separation device and a volume of whole blood withdrawn from the subject. See §X.D.1; EX1005, 41:8-44:32; EX1006, 12:22-25; 17:19-24; EX1008, 2:45-49.

E. Ground 5: Claims 4 and 15 are obvious over Lavender in view of Takagi, Min, and Turgut

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1. Claim 4: A method according to claim 1, further comprising: determining a volume of anticoagulant within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device.

185. A POSITA would have recognized that determining the total volume of anticoagulant in the collected plasma component based on the change in volume within the anticoagulant container would not account for any anticoagulant in the blood separation device that has not yet flowed into the plasma collection container. *See* §X.C.1. A POSITA would have also recognized that accounting for the anticoagulant remaining in the blood separation device would reduce errors and increase the accuracy of the determined anticoagulant volume in the plasma collection container.

186. A POSITA would have found it obvious and would have been motivated to combine Lavender, Takagi, and Min with Turgut's teaching of a volume detector to determine a total volume of fluid within a blood separation system, such as a separation chamber of a centrifuge used to separate blood into components. EX1011, [0073].

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

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188. Turgut's separation system is structurally similar Lavender's (See Fig. 20) and is used to separate blood into different components. EX1011, [0052]-[0068], Fig. 1A. Therefore, it would have been obvious, and a POSITA would have been motivated, to modify Lavender's blood fractionating system (including Takagi's centrifuge, *see* §X.D.1., above) as modified by Min, which monitors the anticoagulant volume input into the system (see §X.C.1), to incorporate Turgut's volume detector to detect the fluid volume remaining in the blood separation device and improve the accuracy of the calculated volume of anticoagulant within the plasma collection container.

189. A POSITA would understand that the volume of plasma plus anticoagulant remaining in the separation device could be determined using Turgut's volume detector to ascertain the total volume remaining in the separation device and subtracting the volume of red blood cells, the volume of red blood cells being equal to the total volume of whole blood introduced to the separation device multiplied by the hematocrit (HCTD). A POSITA would then determine the volume of anticoagulant remaining within the separation device by multiplying the volume of plasma plus anticoagulant by the plasma dilution factor times the conversion factor ($i.e., PDF * CF$). A POSITA would recognize that the determined volume of anticoagulant remaining within the blood component separation device should be

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subtracted from the amount of anticoagulant supplied to the blood component separation device to more accurately estimate the total amount of anticoagulant within the plasma collection container.

190. The combined system discloses determining a volume of anticoagulant within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device.

2. Claim 15: A system according to claim 11, an optical sensor located on the blood component separation device and configured to monitor the contents of the blood component separation device and determine if a volume of anticoagulant remains within the blood component separation device, the calculated volume of anticoagulant in the collected plasma component being based, at least in part, on the volume of anticoagulant within the blood component separation device.

191. See §X.E.1. A POSITA would recognize that the volume detector of Turgut may be an optical sensor, similar to the optical sensor 15 included in Takagi's centrifuge 20. EX1004, ¶0051. It was generally known by a POSITA at the time of the effective filing date of the '652 patent that a volume detector may be an optical sensor.

XI. Availability for Cross-Examination

192. In signing this declaration, I recognize that the declaration will be filed

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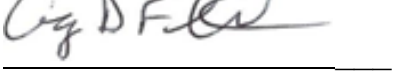
as evidence in a case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I also recognize that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, I will appear for cross examination within the United States during the time allotted for cross examination.

XII. Right to Supplement

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

XIII. Jurat

194. 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:	By
February 9, 2026	 Dr. Gary D. Fletcher

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