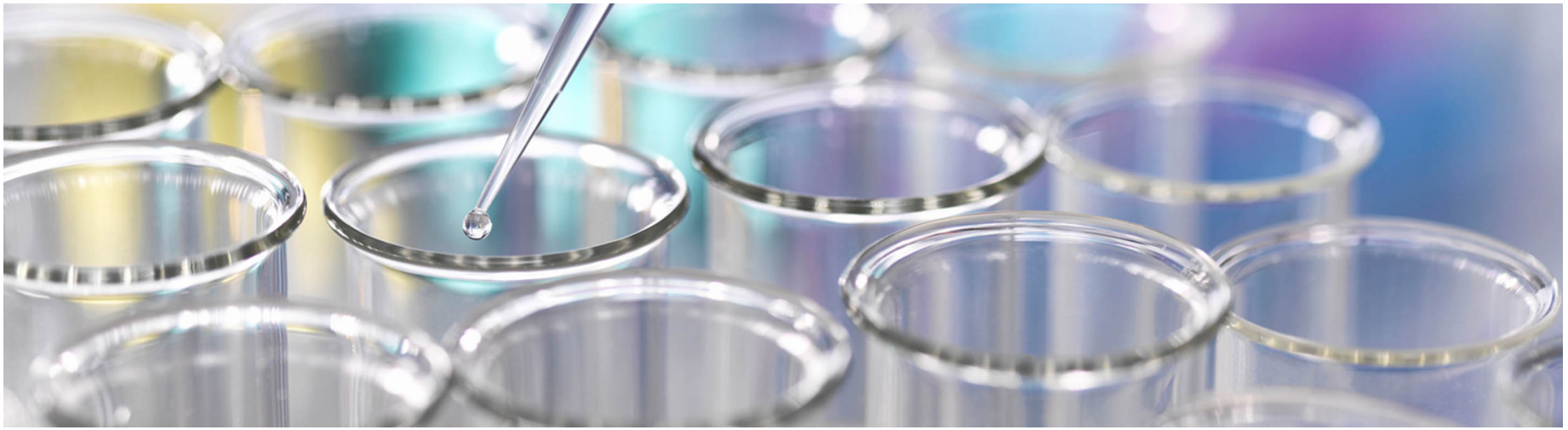
PLASMA COLLECTION, FRACTIONATION, & FINE-FINISHING OF IMMUNOGLOBULIN TREATMENTS

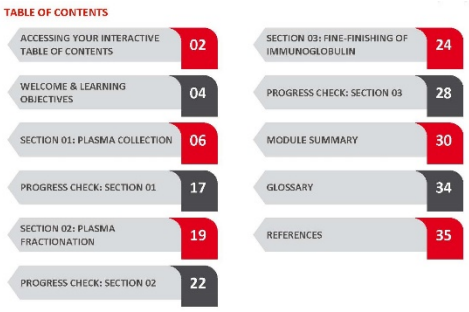
RARE DISEASE HUB

C-ANPROM/UK/IG/0030 February 2022



ACCESSING YOUR INTERACTIVE TABLE OF CONTENTS

For All Devices Using Adobe Acrobat Reader or Nuance Power PDF



To quickly navigate across different parts of the module, click on the section titles in the Table of Contents on page 3.

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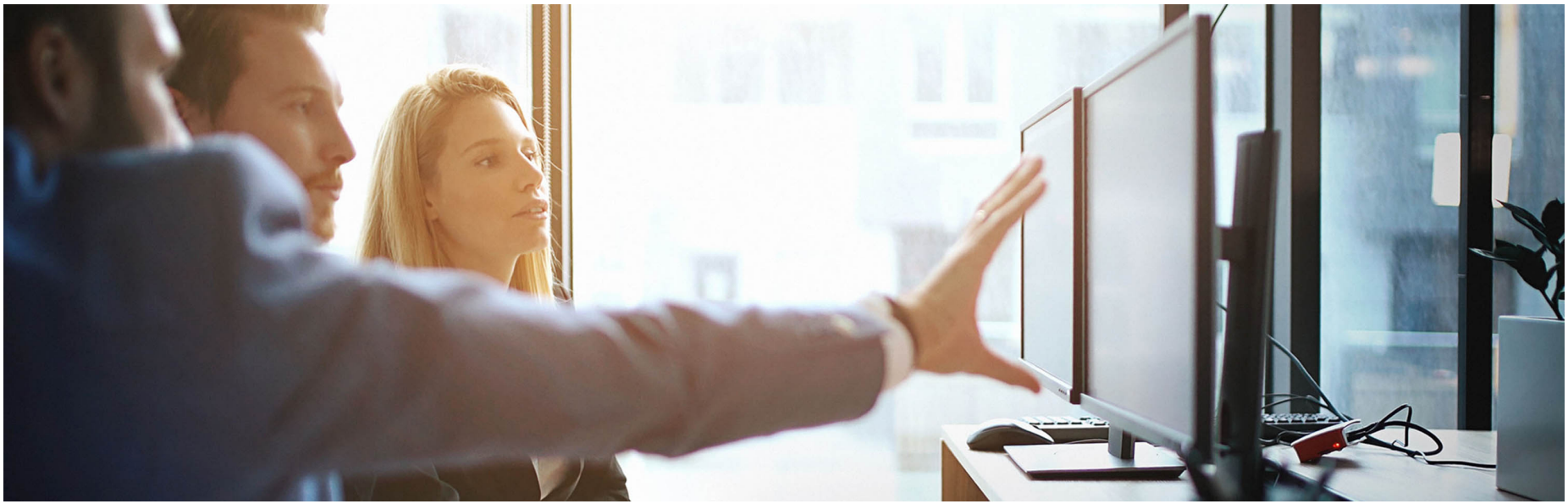
TABLE OF CONTENTS



WELCOME & LEARNING OBJECTIVES

Upon completion of this module, you will be expected to demonstrate that you can…

- Describe the plasma collection process used for Takeda's plasma-derived therapeutic products
- Explain how collected plasma is fractionated for Takeda's plasma-derived therapeutic products
- Explain Takeda's fine-finishing process for IG treatments

Welcome to the Plasma Collection, Fractionation & Fine-Finishing of Immunoglobulin (IG) Treatments module!

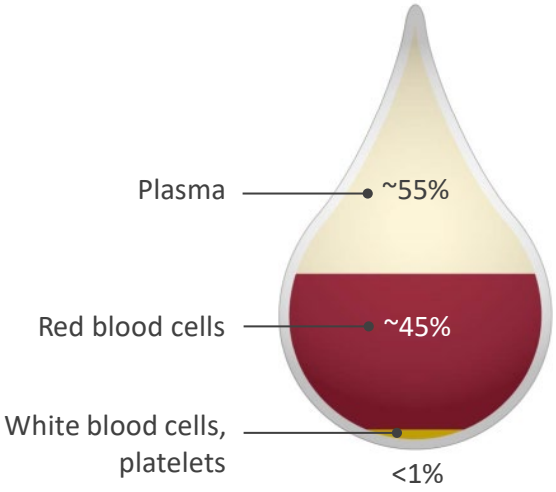
Alexia is considering becoming a plasma donor. She has a brother who relies on IG replacement treatment to manage his primary immunodeficiency (PI), and she knows that his treatment is derived from human plasma. Alexia would like to learn about the plasma collection process including the screening criteria used to qualify donors. She is also curious to know how the collected plasma is then processed into IG therapeutic products.

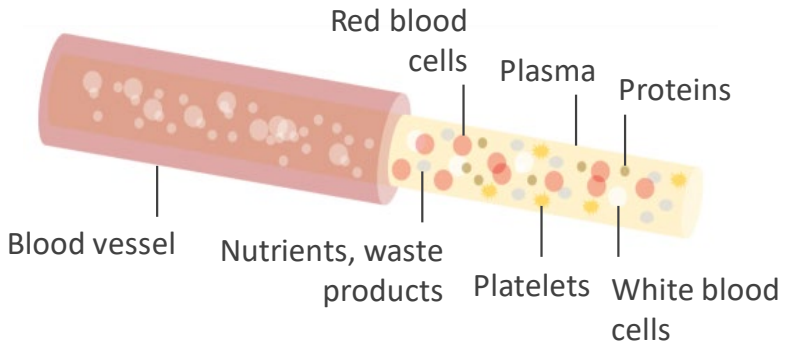
In this course you will learn how plasma-derived therapeutic products are produced, including the processes of plasma collection, fractionation, and fine-finishing.

SECTION 01:
PLASMA COLLECTION

Introduction to Plasma Collection

- **Plasma** is a component of blood, making up approximately 55% of total blood volume
- Plasma transports blood cells throughout the body along with nutrients, waste products, **antibodies**, clotting proteins, hormones, and other proteins
- Specific proteins of human plasma are fractionated, concentrated, and purified to produce plasma-derived treatments
- Plasma-derived therapeutic products are produced from donor plasma from qualified donors





Plasma
A major constituent of total blood volume that has a role in blood transport and chemical reactions.

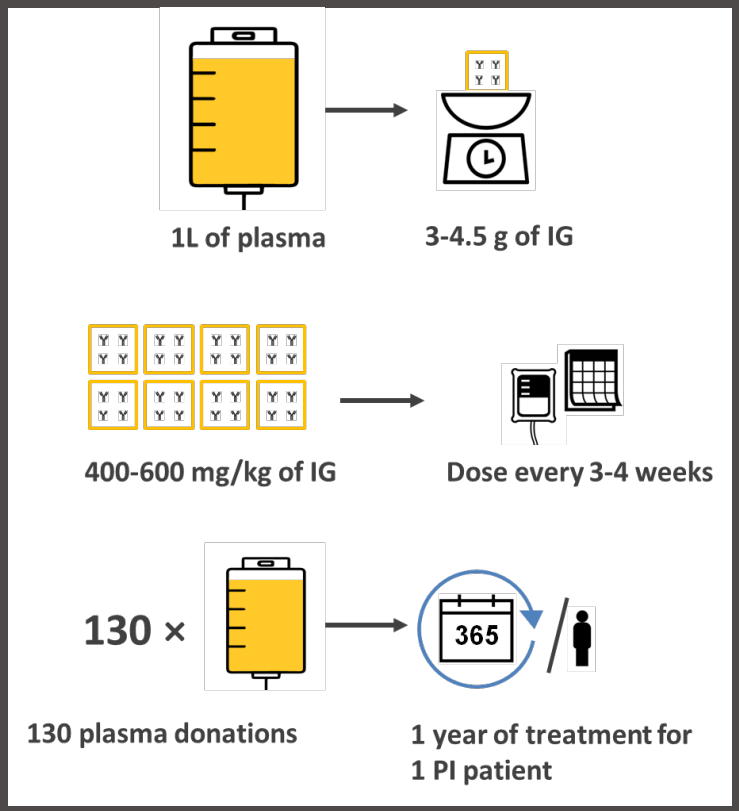
Antibody
Immunoglobulin molecule produced by B lymphocytes (also known as B cells) that combine specifically with an **antigen** to destroy or control it.

Antigen
Any substance that is capable of activating an immune response or binding with an antibody.

Introduction to Plasma Collection (Cont.)

DID YOU KNOW?

- One litre of plasma from qualified donors yields roughly 3.0–4.5 g of **immunoglobulin** (IG)
- The recommended starting dose of intravenous IG (IVIG) for PI patients 400–600 mg/kg every 3–4 weeks
- It takes 130 plasma donations to process enough IVIG to provide a therapeutic dose for one patient with PI for one year



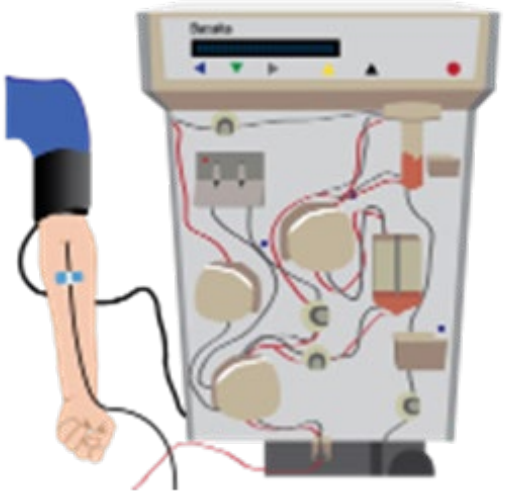
Immunoglobulin (IG)
Any of a diverse group of plasma polypeptides that binds antigenic proteins and serves as one of the body's primary defences against disease. There are five types of immunoglobulins (IgA, IgD, IgE, IgG, and IgM). Also known as antibodies. IG (or Ig) is frequently used as a general term when referring to treatment with IgG.

Methods of Plasma Collection

Plasma can come from either what is called **source plasma** or **recovered plasma**.

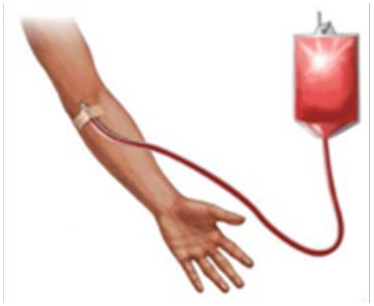
Source Plasma

- With source plasma, donors can donate plasma via a method called **plasmapheresis**, whereby blood plasma is obtained without depleting the donor of other blood constituents
- With plasmapheresis, a healthy plasma donor can donate up to twice a week with at least 24 hours between donations
- The plasma is separated from the whole blood and then the rest is immediately returned to the donor's circulatory system
- A considerable amount of plasma (approximately 600–800 mL) can be collected from each donation
- The vast majority of plasma used to make Takeda's plasma-derived products comes from source plasma



Recovered Plasma

- Recovered plasma refers to plasma obtained from whole blood donations
- Volunteers can donate a maximum of three times per year for females and four times per year for males, and approximately 250 mL of plasma can be obtained per donation



Source Plasma
Plasma collected through plasmapheresis, in which whole blood is withdrawn and separated into plasma and other elements. The plasma is retained, while the cellular blood components are returned back to the donor.

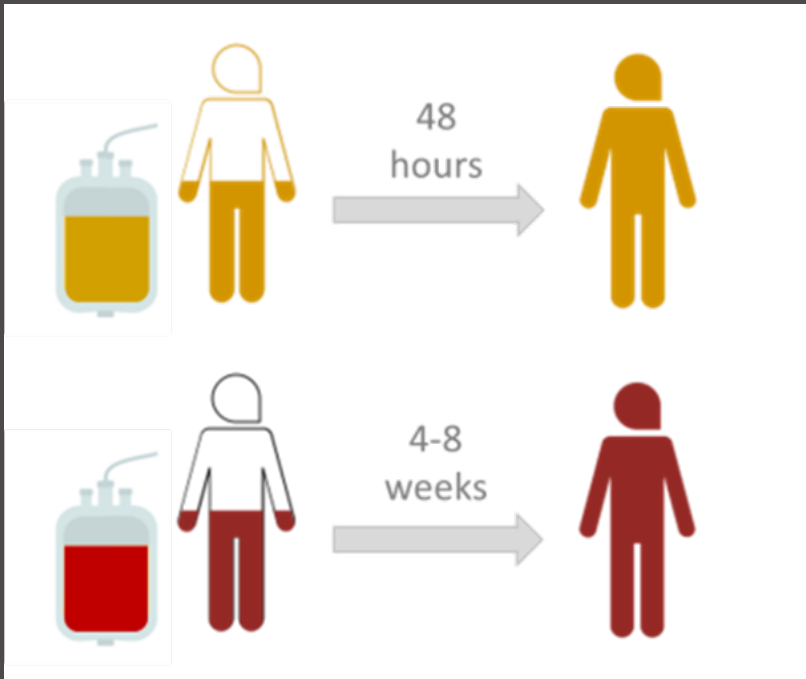
Recovered Plasma
Plasma obtained from whole blood donations.

Plasmapheresis
Process in which whole blood is withdrawn and separated into plasma and other elements. The plasma is retained, while the cellular blood components, such as red blood cells, are returned back to the donor.

Methods of Plasma Collection (Cont.)

DID YOU KNOW?

- Plasmapheresis technology is what allows plasma donors to donate more frequently than whole blood donors
- Plasmapheresis removes only plasma and returns the rest of the blood components (such as red blood cells and platelets) back to the donor
- Humans regenerate plasma within 48 hours, allowing donors to recover from their donation relatively rapidly and donate again within the same week if they choose
- Whole blood donation removes red blood cells, which take approximately 4–8 weeks to regenerate



BioLife Plasma Services

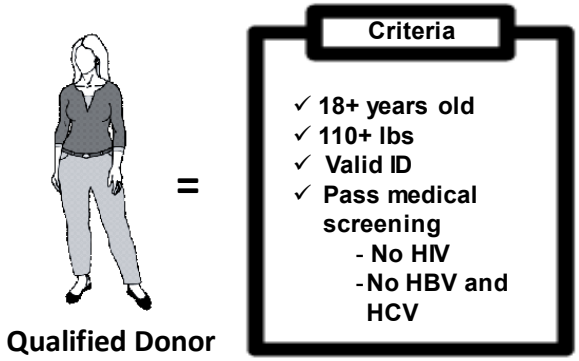
The majority of Takeda's source plasma comes from plasmapheresis centres operated by BioLife Plasma Services, which is part of Takeda Pharmaceutical Company Limited.

- BioLife maintains the highest quality industry standards when collecting plasma that is processed into plasma-based treatments
- As of mid 2020, there are over 120 donation centres in the US and more than 30 donation centres across Austria, Hungary and the Czech Republic
- BioLife Plasma Services compensates donors for their time

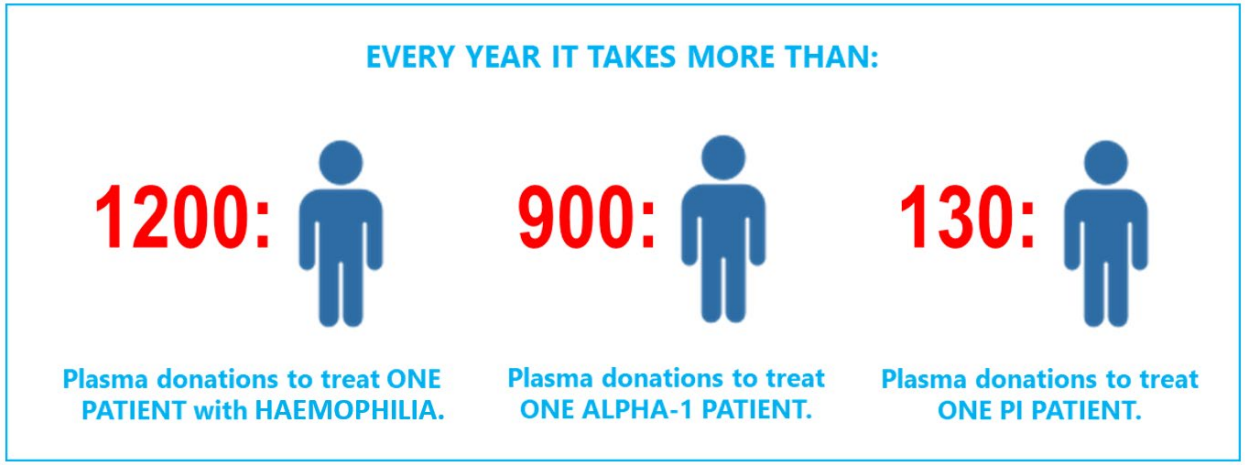
Criteria for Good Plasma Donors

To ensure product quality and the safety of both donors and patients receiving life-saving plasma products, plasma donors must meet certain criteria:

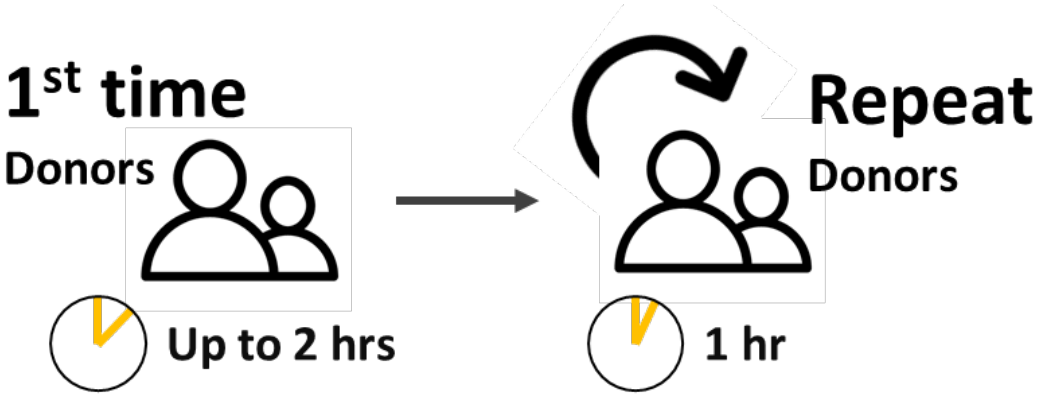
- Potential donors must be at least 18 years of age, weigh at least 7 stones and 12 pounds (110 pounds or 50kg), and provide government-issued documentation to confirm identity
- They must then undergo two separate medical screenings as well as testing for human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) on two separate donations
- Only after passing results from both medical screenings and negative test results can an individual qualify as a donor



Donating plasma is essential for saving lives. Plasma is used to make medications that are vitally important to treat certain medical conditions, including blood disorders, immunodeficiency, extensive burns, and debilitating cancers.



Plasma Donor Experience



- During their initial visit, donors undergo a physical examination and their medical history is recorded
- During subsequent visits, a donor's vital signs are checked, they answer further questions regarding their medical history and their haematocrit (the percentage of blood volume occupied by red blood cells) and plasma protein levels are checked
- During the actual collection of source plasma, whole blood is separated into individual components using a specialised device. This process, known as plasmapheresis, separates red blood cells and other components in the blood, which are then returned to the donor
- The entire plasma donation process can take up to 2 hours for new donors
- For repeat donors, the entire donation session usually takes about one hour
- Plasma donors can donate up to two times in a seven-day period, with at least one day between donations

Donor Testimonials

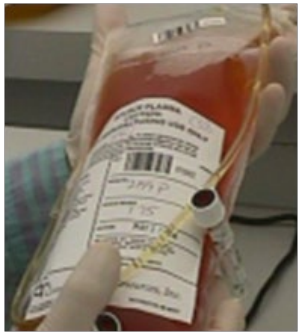


Jason	Janet	Bryan
“Since I’ve started donating plasma, I feel like I'm making a difference in someone's life. The staff are very helpful. I was nervous during my first time donating because of stories I’d heard about donating. Well, those stories couldn't be further from the truth. Not only do I feel like I'm making a difference, but I get compensated for it as well. This experience has been awesome and I plan on continuing to donate for the better of people that need it.”	“I donated plasma regularly years ago, and stopped when my iron levels kept dropping. I recently started donating again. A week ago, my husband was hospitalised. He has been treated both times with infusions. The infusions were derived from the plasma of thousands of donors. I just wanted you all to know that besides the payments we get from donating, this really does save lives; and, once in a while it comes right back to you one way or another.”	“I never have been a big fan of needles, but I've looked beyond that. It makes me feel good knowing that I am helping save someone's life. It also helps me make some extra money on the side. I donate twice a week, but I always look forward to it.”

Appropriate Handling Throughout the Source Plasma Collection Process

- Source plasma is collected in bags or bottles and frozen within 30 minutes of collection to a temperature of approximately –30°C
- Samples from each donation are sent to a BioLife laboratory to be tested
- Each plasma donation is screened for infection with viruses such as hepatitis and HIV

- Plasma donations from applicant donors are held for 60 days prior to further processing
- An applicant donor must return to provide a second donation within six months of the first donation before the plasma from that donor can be considered for use
- If the applicant donor successfully completes a second round of screening interviews and laboratory tests the donor becomes a "qualified donor" and his or her plasma may be considered for use
- After the plasma is collected, it is frozen, tested and shipped to processing sites for **fractionation**

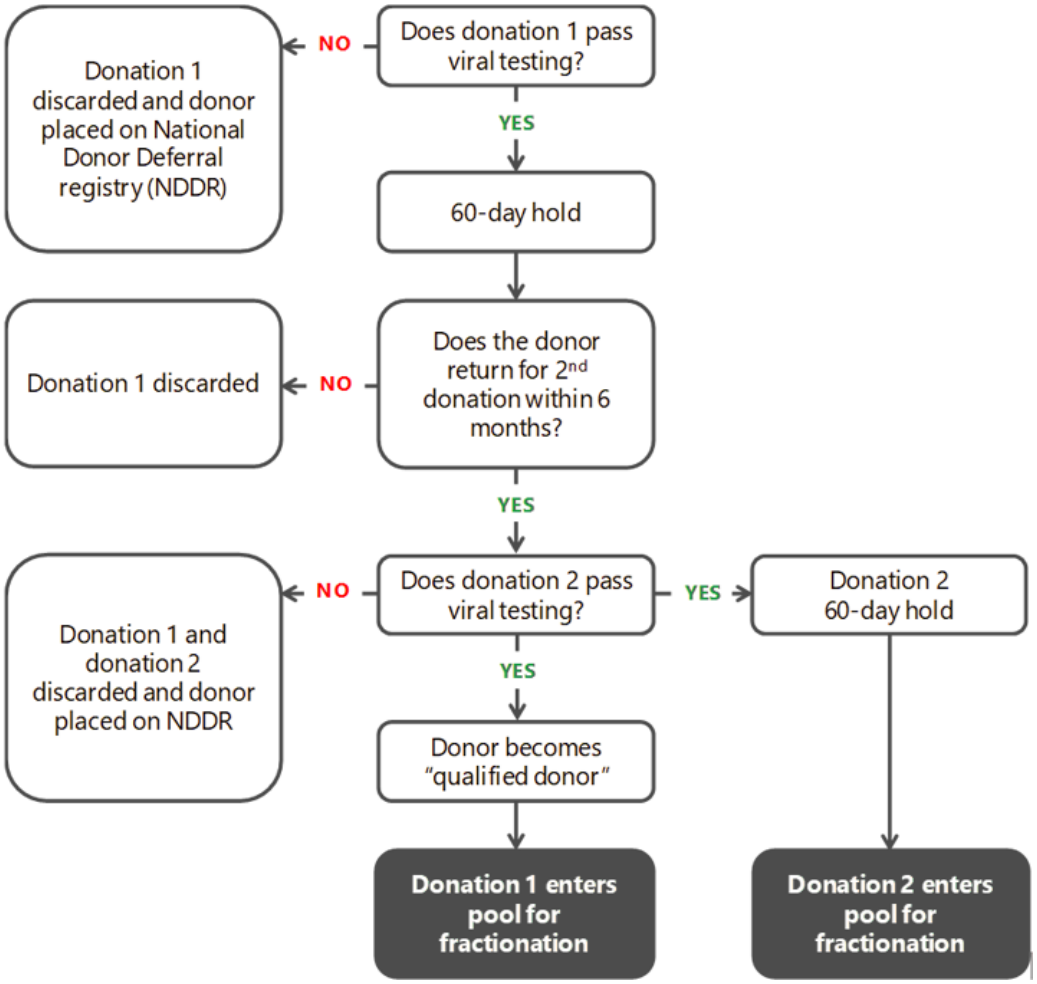


DID YOU KNOW?

Plasma donations are held for 60 days (inventory hold) prior to further processing. This measure allows for the retrieval, prior to processing, of plasma units from previously qualified donors who are later found to have unacceptable results.

Fractionation
Separation of a mixture into its components in an effort to isolate a substance (protein) of interest.

Appropriate Handling Throughout the Source Plasma Collection Process (Cont.)



PROGRESS CHECK

QUESTION ONE

Think about how you would complete the following question, then select the Check Your Answer button.

Which of the following criteria need to be met to become a qualified donor?

A Must be employed or an adult student

B Must provide valid legal identification

C Must be between the ages of 18 and 40 years

D Must pass two separate medical screenings and testing for HIV, HBV and HCV on two different donations

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION ONE

Which of the following criteria need to be met to become a qualified donor?

A Must be employed or an adult student

B Must provide valid legal identification

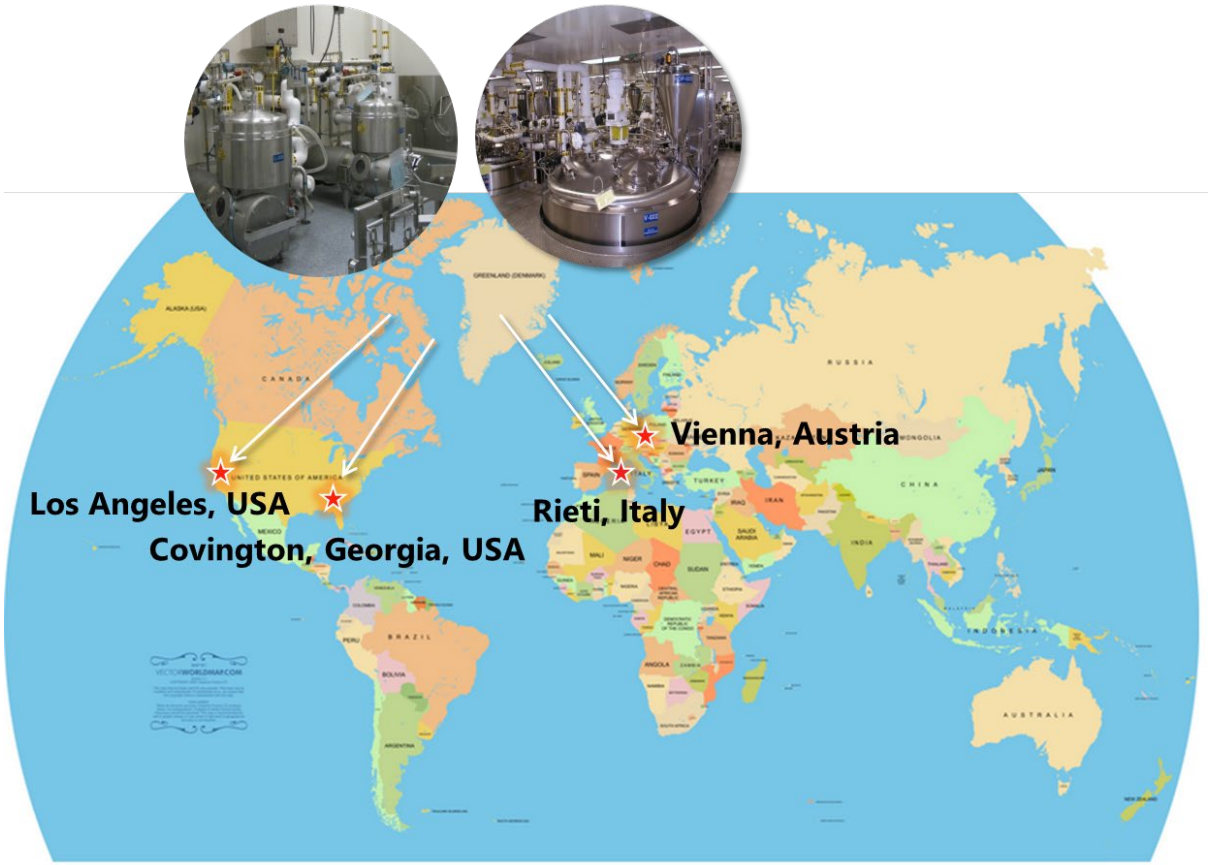
C Must be between the ages of 18 and 40 years

D Must pass two separate medical screenings and testing for HIV, HBV and HCV on two different donations

SECTION 02:
PLASMA FRACTIONATION

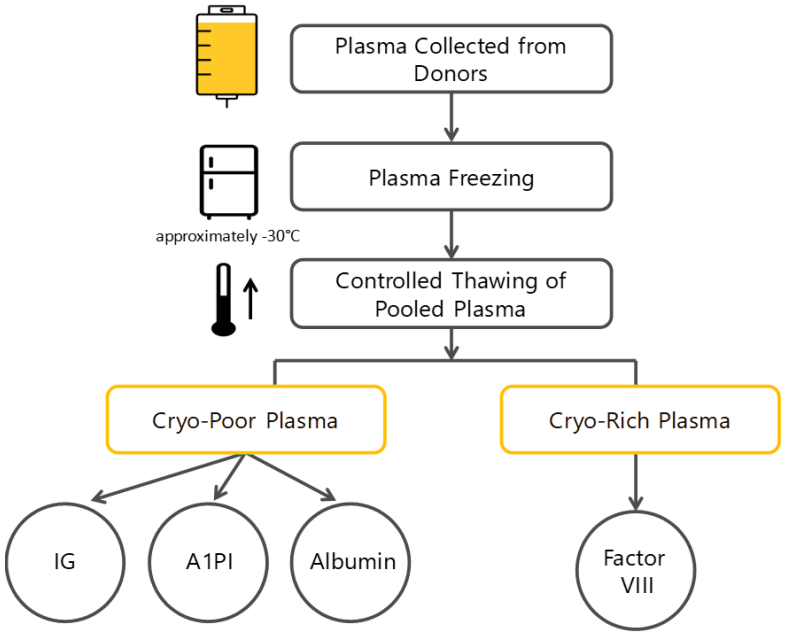
Takeda's Fractionation Facilities

After the plasma is collected and tested, it is sent to a Takeda facility in either Los Angeles, Covington/Georgia (both USA); Vienna (Austria); or Rieti (Italy) where it undergoes a process called "fractionation." This is a method for separating specific proteins out from plasma.



Fractionation Process

- Source plasma is frozen after collection to a temperature of approximately –30°C and before fractionation the frozen plasma undergoes controlled thawing at 0.2 to 4.0°C for a first separation of proteins (**cryo-precipitation**)
- During plasma fractionation, temperature, pH, and ethanol concentration are altered to precipitate specific proteins
- **Centrifugation** or **filtration** methods are used to separate the proteins



A1PI = alpha$_1$-proteinase inhibitor

- First, the plasma is separated into cryo-poor plasma and cryo-rich plasma
  - Cryo-rich plasma is used to produce factor VIII treatments
  - Cryo-poor plasma is further separated into the fractions used to produce IG, albumin, and alpha$_1$-proteinase inhibitor treatments including a number of additional coagulation factor and inhibitor products
- After the fractionation process, these bulk proteins are packaged and shipped to other facilities for fine-finishing

Cryoprecipitation
Separation as a solid from a solution by cooling the solution (e.g., separation of factor VIII from plasma).

Centrifugation
The process of spinning liquids under high speeds to separate heavy or dense particles from lighter liquids.

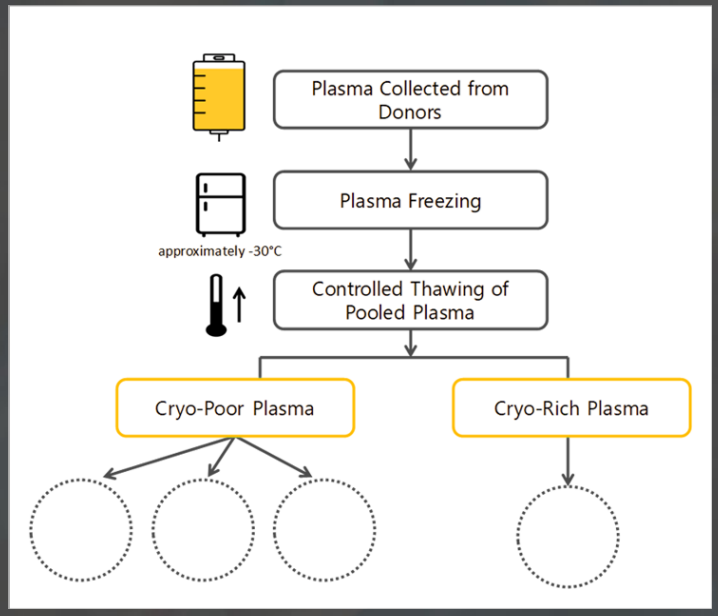
Filtration
Particle removal from a solution by allowing the liquid portion to pass through a membrane or barrier containing holes or spaces.

PROGRESS CHECK

QUESTION TWO

Think about how you would complete the following question, then select the Check Your Answer button.

Fill in the blanks on the diagram below representing the fractionation process.



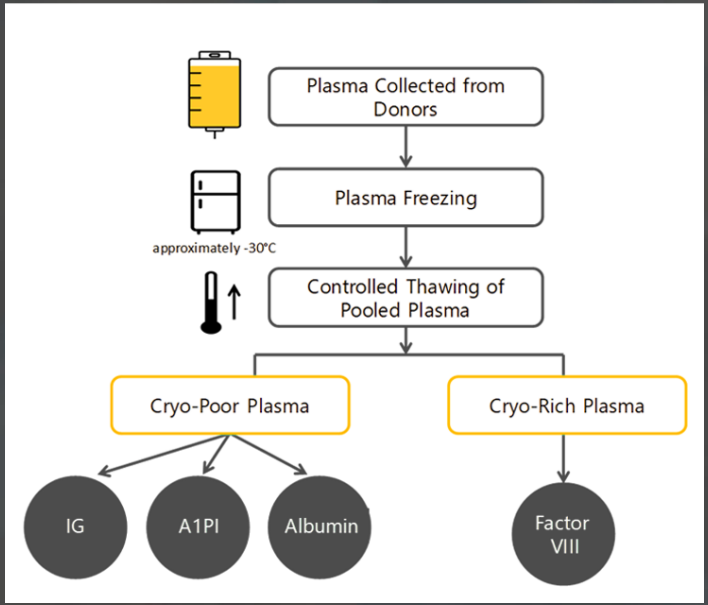
Options:
Albumin, A1PI, Cryo-poor plasma, Cryo-rich plasma, Factor VIII, IG

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION TWO

Fill in the blanks on the diagram below representing the fractionation process.



SECTION 03:
FINE-FINISHING OF IMMUNOGLOBULIN

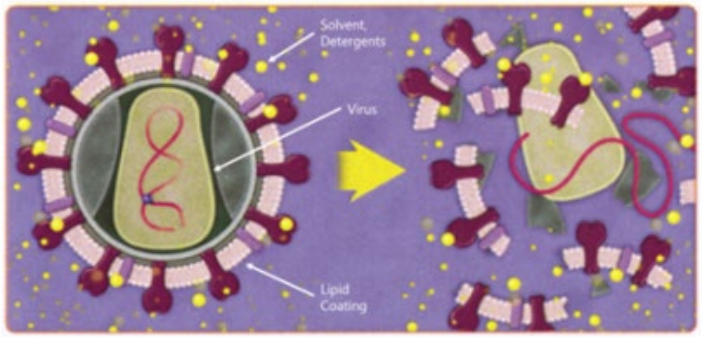
Pathogen Inactivation and Removal

Takeda manufacturing processes utilise one or more virus inactivation processes to help improve the safety profile of the finished product.

The finishing processes include three dedicated and independent **pathogen** inactivation and removal steps:

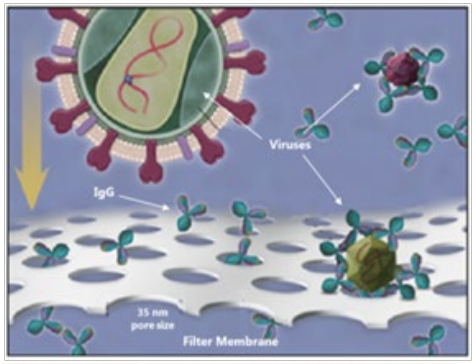
Solvent/Detergent (S/D) Treatment:

- Is a viral inactivation step that involves incubating the IG protein solution with one solvent and one or two detergents
- Disrupts the outer coating of lipid-enveloped viruses (e.g., HIV, HBV, HCV, Ebola, and SARS) to inactivate virus infectivity



*35 nm **Nanofiltration**:*

- Takeda's immunoglobulin solutions are passed through filter devices of a pore-size of 35 nm to filter out viruses
- Contributes to the removal of both enveloped and non-enveloped viruses such as hepatitis A and parvovirus; concomitant use of specific antibodies help remove small viruses



Low pH/Elevated Temperature:

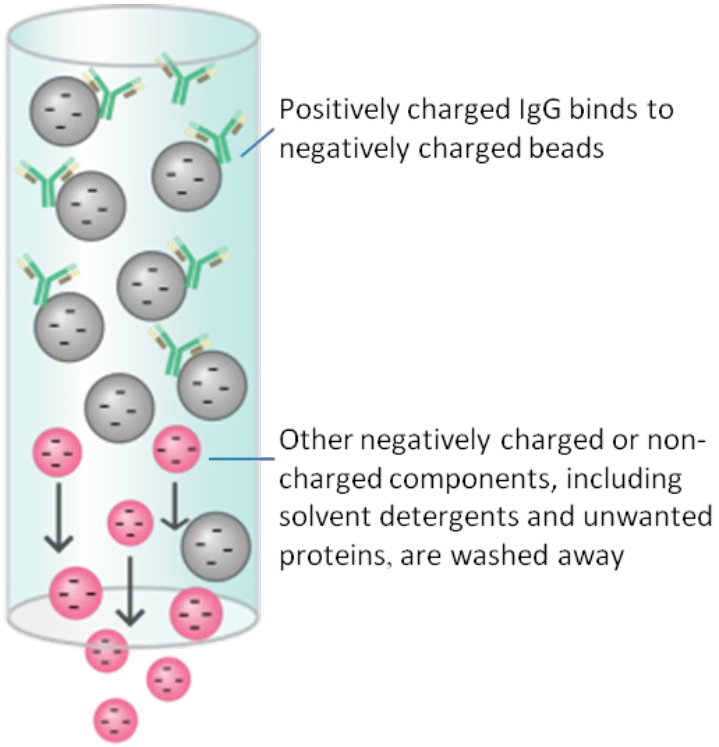
- Involves heating the final product in vials to 30–32°C at a low pH of 4.4–4.9 for 21–24 days
- Inactivates lipid-enveloped viruses and some non-enveloped viruses

Pathogen
Any microorganism capable of producing disease.

Nanofiltration
A pathogen removal filtration procedure using filters with pore sizes of a few nanometres

Ion Exchange Chromatography

- **Ion exchange chromatography** is a purification step used to extract proteins of interest from a plasma fraction or to eliminate unwanted proteins
- It separates proteins based on differences in electrical charge, and results in more purified and concentrated IG protein
- The positively charged **immunoglobulin G (IgG)** precipitate binds to the negatively charged ion exchange chromatography column, whereas other components do not bind, and are washed away



Ion exchange
As part of Takeda's manufacturing process for IG, ion exchange chromatography involves negatively charged beads in a column that help to purify and concentrate the IgG and eliminate the non-IgG components.

Chromatography
Method of separating two or more substances in a liquid or gas by their removal at different rates depending on their solubility or capacity for adsorption.

Immunoglobulin G (IgG)
The principal immunoglobulin in human serum. It is the major antibody for antitoxins, viruses, and bacteria. It also activates complement and serves as an opsonin.

Formulations

- Takeda offers finished IG products with varying IgG protein concentrations (e.g., 10%, 20%)
- The different concentrations are produced through different ultrafiltration or diafiltration steps to concentrate the IG solution to different levels

Final Packaging

- Takeda's finished IG products are packaged into bottle or vial sizes appropriate for each brand, and labelled with the expiration date; they are then kept under refrigeration until they reach patients
- Finished IG products are shipped to warehouses from where they are then shipped to specialty pharmacies and infusion centres or clinics, distributors, and then finally provided to patients
- Every package of Takeda IG product is labelled with a lot number so that the product can be traced back to the donors that contributed to that lot; this permits Takeda to trace a specific package of IG product that may be associated with a reported product complaint or **adverse event** all the way back to the donation source

Adverse event
Any undesirable medical event that occurs during treatment with a pharmaceutical product which may or may not relate to treatment with the therapeutic product.

PROGRESS CHECK

QUESTION THREE

Think about how you would complete the following question, then select the Check Your Answer button.

Using the available options, fill in the blanks of the following sentences. An option may be used more than once.

1. Solvent/detergent treatment is a _____ step.
2. Nanofiltration is used as a _____ step.
3. Low pH and elevated temperature is a _____ step.
4. Ion chromatography is used as a _____ step.

OPTIONS:
viral removal, viral inactivation, purification

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION THREE

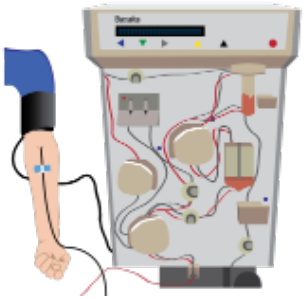
Using the available options, fill in the blanks of the following sentences. An option may be used more than once.

1. Solvent/detergent treatment is a **viral inactivation** step.
2. Nanofiltration is used as a **viral removal** step.
3. Low pH and elevated temperature is a **viral inactivation** step.
4. Ion exchange chromatography is used as a **purification** step.

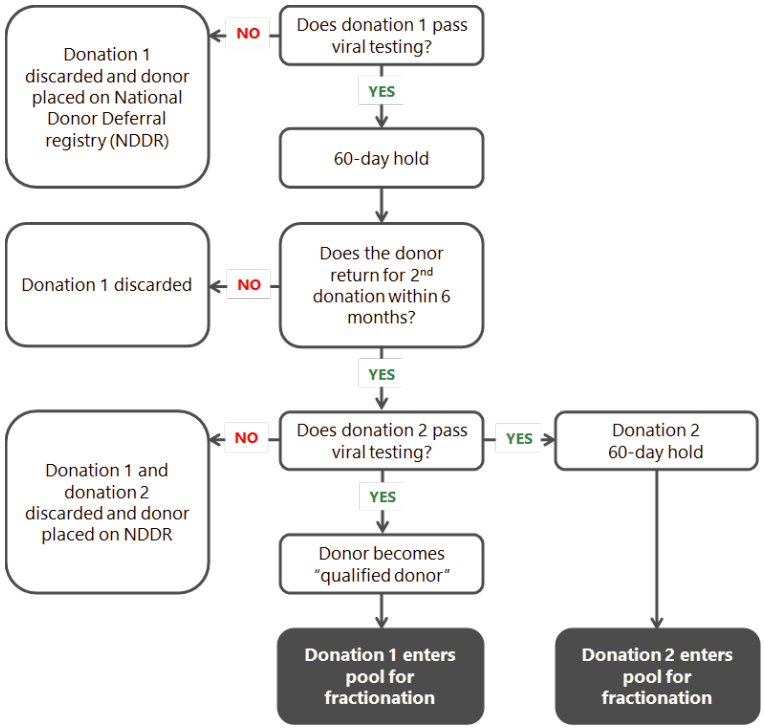
Module Summary

Plasma Collection

- Plasma-derived treatments are produced from the protein component of donated human plasma from qualified donors
- The majority of plasma used to make Takeda's plasma-derived products comes from source plasma, whereby donors donate via plasmapheresis
- The majority of Takeda's source plasma comes from plasmapheresis centres operated by BioLife Plasma Services



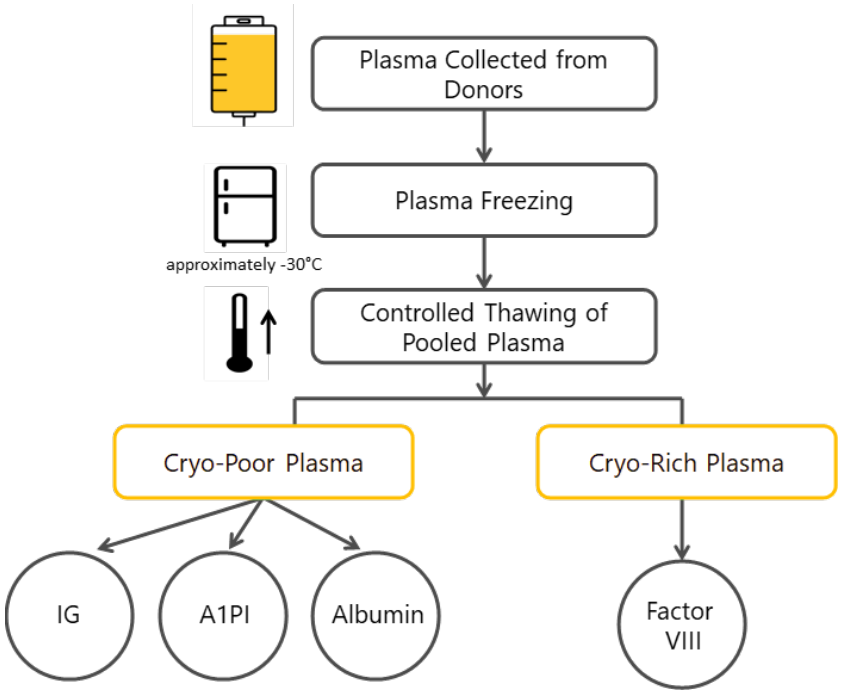
- Potential donors must pass two separate medical screenings and testing for HIV, HBV and HCV on two different donations before they become a qualified donor
- Plasma donations from qualified donors are held 60 days prior to further processing
- All plasma donations are screened for viruses such as HIV, HBV and HCV



Module Summary (Cont.)

Plasma Fractionation

- Fractionation is a method for separating proteins from plasma
- Temperature, pH, and ethanol concentration are altered to selectively precipitate proteins of interest. Centrifugation or filtration methods are used to separate the proteins
- Results in separate fractions for factor VIII, immunoglobulin, alpha1-proteinase inhibitor, albumin and a number of additional coagulation factor and inhibitor products.

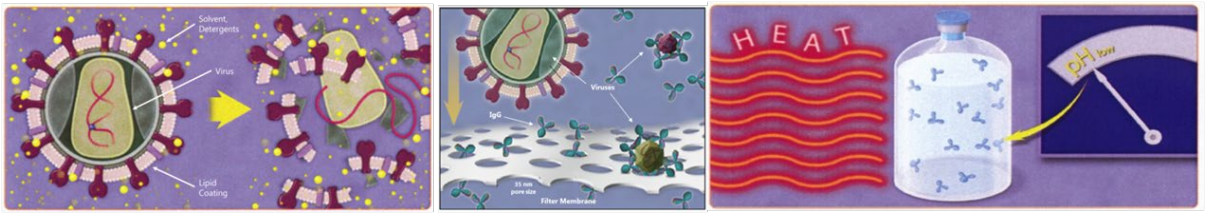


Module Summary (Cont.)

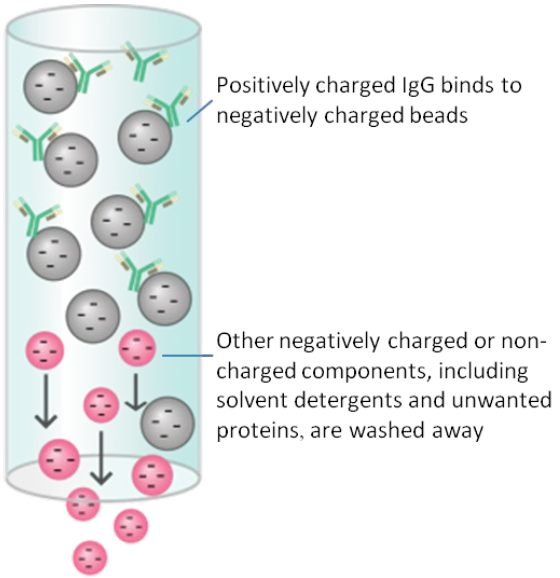
Fine-Finishing of Immunoglobulin

IG proteins obtained from the fractionation process undergo a final set of finishing processes to become IG products:

- Pathogen removal/inactivation:
  - Solvent/detergent treatment
  - 35 nm nanofiltration
  - Low pH/elevated temperature



- Ion-exchange chromatography:
  - Separates plasma components based on differences in electrical charge
  - Positively charged IgG binds to the negatively charged ion exchange chromatography column whereas other plasma components are washed away
  - Results in more purified and concentrated protein



Module Summary (Cont.)

Fine-Finishing (Cont.)

- Formulations
  - IG treatments of varying IgG protein concentrations are produced during fine-finishing through different ultrafiltration or diafiltration steps to concentrate the IG solution to different levels

- Final Packaging
  - Takeda's finished IG products are packaged into bottle/vial sizes appropriate for each brand, and labelled with the lot number and expiration date
  - Takeda's IG products are produced with a lot number so that the product can be traced back to the donors that contributed to that lot

GLOSSARY

Adverse event
Any undesirable medical event that occurs during treatment with a pharmaceutical product which may or may not relate to treatment with the therapeutic product.

Antibody
Immunoglobulin molecule produced by B lymphocytes (also known as B cells) that combine specifically with an antigen to destroy or control it.

Antigen
Any substance that is capable of activating an immune response or binding with an antibody.

Centrifugation
The process of spinning liquids under high speeds to separate heavy or dense particles from lighter liquids.

Chromatography
Method of separating two or more substances in a liquid or gas by their removal at different rates depending on their solubility or capacity for adsorption.

Cryoprecipitation
Separation as a solid from a solution by cooling the solution (e.g., separation of factor VIII from plasma).

Filtration
Particle removal from a solution by allowing the liquid portion to pass through a membrane or barrier containing holes or spaces.

Fractionation
Separation of a mixture into its components in an effort to isolate a substance (protein) of interest.

Immunoglobulin (IG)
Any of a diverse group of plasma polypeptides that binds antigenic proteins and serves as one of the body's primary defences against disease. There are five types of immunoglobulins (IgA, IgD, IgE, IgG, and IgM). Also known as antibodies. IG (or Ig) is frequently used as a general term when referring to treatment with IgG.

Immunoglobulin G (IgG)
The principal immunoglobulin in human serum. It is the major antibody for antitoxins, viruses, and bacteria. It also activates complement and serves as an opsonin.

Ion exchange
As part of Takeda's manufacturing process for IG, ion exchange chromatography involves negatively charged beads in a column that help to purify and concentrate the IgG and eliminate the non-IgG components.

Nanofiltration
A pathogen removal filtration procedure using filters with pore sizes of a few nanometres.

Pathogen
Any microorganism capable of producing disease.

Plasma
A major constituent of total blood volume that has a role in blood transport and chemical reactions.

Plasmapheresis
Process in which whole blood is withdrawn and separated into plasma and other elements. The plasma is retained, while the cellular blood components, such as red blood cells, are returned back to the donor.

Source Plasma
Plasma collected through plasmapheresis, in which whole blood is withdrawn and separated into plasma and other elements. The plasma is retained, while the cellular blood components are returned back to the donor.

Recovered Plasma
Plasma obtained from whole blood donations.

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