Takeda's legacy and commitment to plasma-based therapeutics

Takeda is a global leader in serving patients with rare and hard-to-treat diseases. Our legacy in this area includes a more than 60-year history in plasma fractionation and manufacturing—with a steadfast commitment to providing life-changing plasma-based therapeutics.[1,2]

A source of plasma-based therapeutics for more than 60 years[1,2]

1954	1968	1982	1986	2003	2007	2008
Albumin	**Factor VIII**	**Activated Prothrombin Complex**	**Immune Globulin**	**Alpha$_1$-Antitrypsin**	**Protein C**	**C-1 Esterase**

Ongoing commitment to innovation

Our heritage in plasma technology extends back to the first commercially available human plasma in the 1950s with the development of therapeutic human albumin. Takeda also has been a reliable source of immune globulin (IG) therapies for more than 30 years.[1,2]

We're committed to building upon our legacy as we work to expand treatment options for rare diseases. As a global leader in rare diseases, Takeda is focused on driving continuous innovation and personalized care through our portfolio of plasma projects.

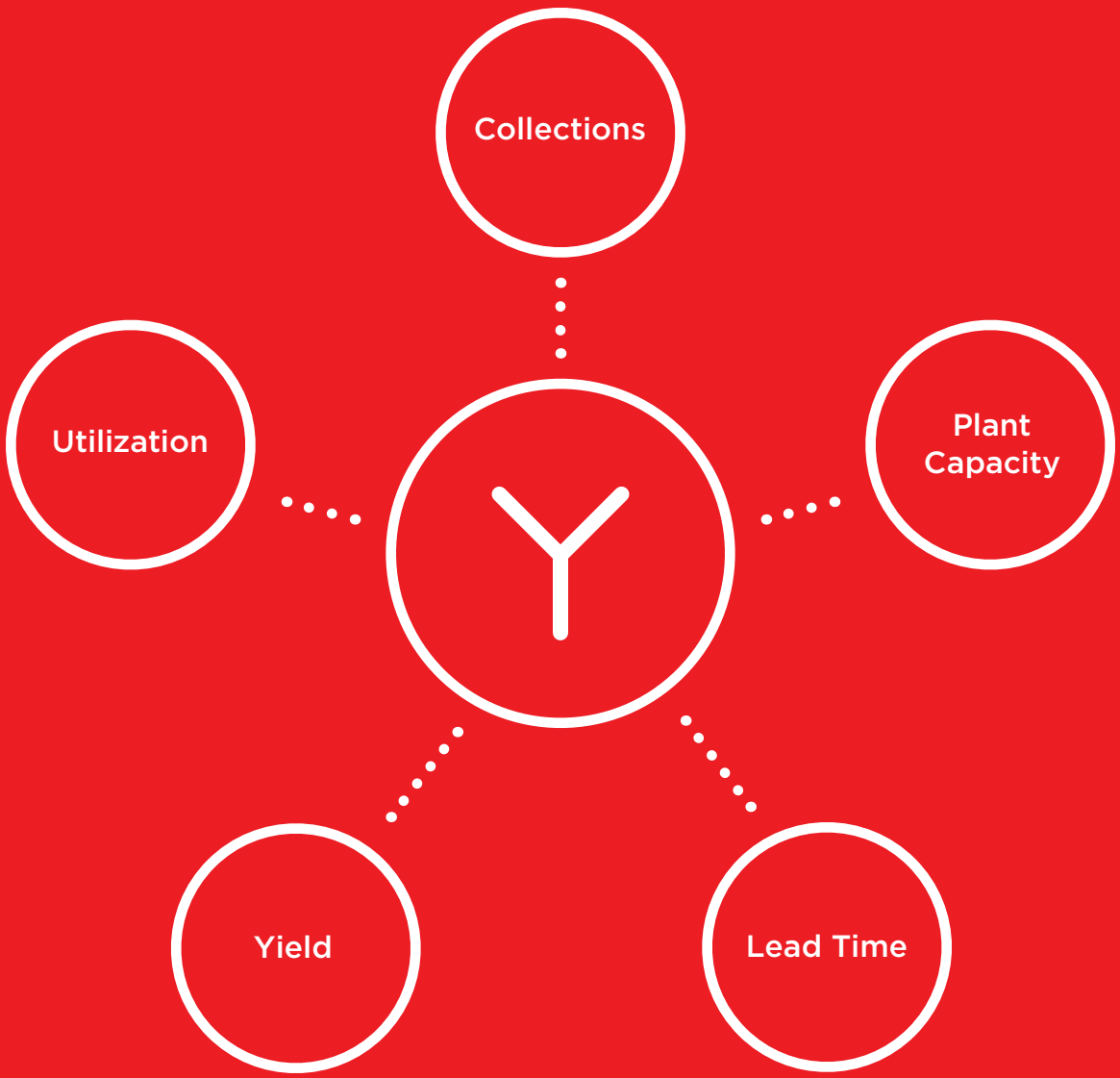
Takeda's rigorous approach to help ensure continued supply

Takeda has the experience and the expertise to confidently manage the end-to-end challenges of developing complex, plasma-based therapeutics—from securing donations to delivering treatment.

Accurately predicting utilization for plasma-based therapeutics, and meeting that demand, can be a complicated process for manufacturers. At Takeda, we conduct rigorous analyses and manage multiple challenges that can impact IG supply, including collections, plant capacity, lead time, yield, and utilization of all plasma products.[3,4]

Approximately 625 to 800 mL of plasma can be safely obtained during each donation.[5]

Factors Impacting IG Supply



Factors Impacting IG Supply

Collections

The amount of plasma that can be collected for fractionation is dependent on the number of centers and donors.[3,4]

Takeda operates more than 100 state-of-the-art BIOLIFE plasma donation centers in the United States to help meet the growing demand for plasma-based therapeutics.[2]

In 2018, Takeda collected an estimated 7.4 million liters of plasma in the United States.[2]

Plant Capacity

Manufacturing plasma-based products involves a series of complex steps—including fractionation, purification, stabilization, and viral inactivation and removal—to ensure the quality and safety of the finished product.[6,7]

Lead Time

Production of IG and other plasma-based therapeutics takes significantly longer than traditional pharmaceuticals or biologics, primarily due to donor screening and complex production procedures.[3,4,8]

As part of the industry's voluntary international standards program, all plasma donations are held in inventory for 60 days before entering the manufacturing process.[7]

Yield

During fractionation, plasma is pooled from multiple donors, purified, and processed to extract plasma proteins that have a demonstrated medical use.[3,7]

IG is the most frequently used plasma component.[9]

Utilization

Increasing demand for plasma-based therapeutics, such as IG, also can impact the supply of other products. Manufacturers typically balance manufacturing costs by increasing the production of all plasma-based therapeutics to help ensure an adequate supply of the product currently in greatest demand.[4]

Amount of IG needed for each patient varies depending on medical use and required dose.[3,5,7,8]

PLASMA-BASED MANUFACTURING STEPS

Plasma donation and screening

Qualified donors must pass 2 screenings within a 6-month period before their plasma donation can be accepted.[3,8]

Fractionation

Plasma yields several products for various conditions, spreading the manufacturing effort across the various products.[3,7]

Purification, stabilization, and viral inactivation and removal

Purification, stabilization, and viral inactivation and removal are critical steps to help ensure product quality and safety.[6]

Final Product

Traditional pharmaceutical manufacturing[10]

Days to weeks

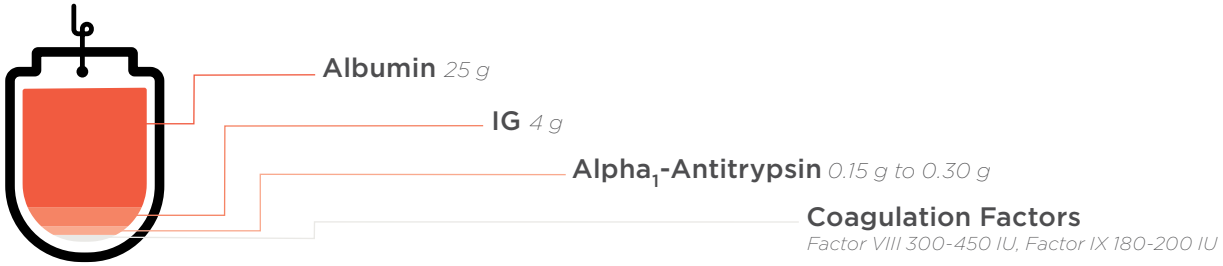
Biologics manufacturing[11]

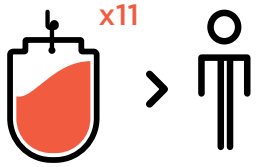
Several weeks to months

Plasma-based product manufacturing[3,8]

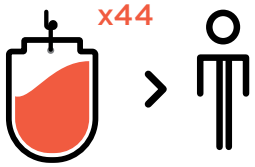
7-12 months from start to finish

PLASMA PROTEIN[3,7]





Primary Immunodeficiency (PI)



Multifocal Motor Neuropathy (MMN)

Unique donations required for a single month of IG treatment for PI or MMN

Approximately 140 unique donations per year would be required to yield 105 L of plasma required to treat an average hypothetical adult PI patient of 70 kg receiving a dose of 35 grams of IG per month.

Four times as many donations would be required to treat a hypothetical adult MMN patient of 70 kg receiving a dose of 140 grams of IG per month.[3,5,7,12]

Continued investment in new manufacturing capacity

To meet growing demand for plasma-based therapeutics, Takeda is focused on optimizing our global manufacturing operation.

As part of this effort, our new state-of-the-art plasma fractionation facility in Covington, GA, will expand capacity by 3 million liters of plasma each year when fully operational—an ~30% increase.[13,14]

The facility received US Food and Drug Administration approval for production of one IG product in June 2018 and albumin in March 2019.[13-15]

Covington, GA—2018

Over $1 billion

investment in state-of-the-art fractionation facility[13]

Multiple Manufacturing Facilities

- Covington, GA
- Lessines, Belgium
- Los Angeles, CA
- Pisa, Italy
- Rieti, Italy
- Vienna, Austria

Committed to advancing the care of patients with MMN

Takeda's commitment to advancing the care of people with multifocal motor neuropathy (MMN) who rely on our therapy is highlighted by our investment in research and development, and plasma collection and fractionation facilities, to ensure a durable and reliable supply of this treatment.[4,7]

References

1. Center for Biologics Evaluation and Research. List of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations to date. https://www.fda.gov/media/89426/download. Accessed February 14, 2020.
2. Marketing Research Bureau. The Plasma Proteins Market in the United States 2018. Revised 2019.
3. *Analysis of Supply, Distribution, Demand, and Access Issues Associated with Immune Globulin intravenous (IGIV), Final Report.* US Dept of Health and Human Services; February 2007.
4. Rhodes RT. Immune globulin: controlling supply and demand. *BioSupply Trends Quarterly*. 2015(Winter):14-18.
5. Jerrard GA, Liu J, Case RC, et al. Implications of weight and body mass index for plasma donation and health. *ISRN Hematol*. 2012;2012:937585.
6. Gelfand EW. Differences between IGIV products: impact on clinical outcome. *Int Immunopharmacol.* 2006;6(4):592-599.
7. Plasma Protein Therapeutics Association. The facts about plasma protein therapy manufacturing. https://www.pptaglobal.org/images/Fact_Sheets/FS_PPT_Manufacturing.pdf. Accessed February 14, 2020.
8. Plasma Protein Therapeutics Association. Plasma. https://www.pptaglobal.org/plasma. Accessed February 14, 2020.
9. Bertolini J, Goss N, Curling J. *Production of Plasma Proteins for Therapeutic Use*. John Wiley & Sons; 2013.
10. Chatterjee S. US Food and Drug Administration. FDA perspective on continuous manufacturing. IFPAC Annual Meeting. January 2012. https://www.fda.gov/media/85366/download. Accessed February 14, 2020.
11. International Alliance of Patients' Organizations. Briefing paper on biological and biosimilar medicines. https://www.iapo.org.uk/sites/default/files/files/IAPO%20Briefing%20Paper.pdf. Accessed February 14, 2020.
12. Léger JM. Immunoglobulin (Ig) in multifocal motor neuropathy (MMN): update on evidence for Ig treatment in MMN. *Clin Exp Immunol.* 2014; 178(suppl 1):42-44.
13. Berman K. Plasma fractionation: the challenge of keeping pace with global IG demand. IG Living. http://www.igliving.com/magazine/articles/IGL_2018-08_AR_Plasma-Fractionation-The-Chellenge-of-Keeping-Pace-with-Global-IG-Demand.pdf. August-September 2018. Accessed February 14, 2020.
14. Data on file. Takeda US Inc. 2018.
15. Takeda receives U.S. FDA approval to manufacture FLEXBUMIN® at new plasma manufacturing facility near Covington, Georgia. Takeda; March 18, 2019. https://www.takeda.com/en-us/newsroom/news-releases/2019/takeda-receives-u.s.-fda-approval-to-manufacture-flexbumin/. Accessed February 14, 2020.

Takeda
Lexington, MA 02421
www.takeda.com
©2020 Takeda Pharmaceutical Company Limited. 1-800-828-2088. All rights reserved.
TAKEDA and the TAKEDA logo are trademarks or registered trademarks of Takeda Pharmaceutical Company Limited.
BIOLIFE is a trademark or registered trademark of Baxalta Incorporated, a Takeda company.
All other product brands or trademarks appearing herein are the property of their respective owners.
US-NON-0591v1.0 05/20