



Managing the immunoglobulin supply gap

Causes, impact and strategies in a challenged market

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Introduction

For thousands of patients worldwide, immunoglobulin (IG) is used to manage chronic diseases, alleviate symptoms and make life livable. Approved by the U.S. Food & Drug Administration (FDA) for use in limited indications, the human-plasma derivative is increasingly being wielded by physicians in the off-label treatment of hundreds of additional conditions.

As the use of IG swells, supplies tighten. The U.S. market is now entering the second year of a short market that has challenged health care providers at all levels. This report

highlights IG and its manufacturing, the roles of distributors and payers, the realities of the worldwide market and efforts to increase supplies of a complex commodity. It also details how Vizient members are coping with supply challenges while maintaining the highest quality of care, and explores how all parties can contribute to the future strategic success in availability of this limited and precious resource.

Plasma-derived therapies

Plasma-derived products are sterile, highly purified preparations made from human plasma pooled from thousands of donors. Plasma — the clear, straw-colored fluid that makes up more than half of human-blood volume — is the source of multiple therapies that have an unequalled power to heal within a spectrum of diseases and disorders. When processed, plasma yields three chief therapeutic substances:

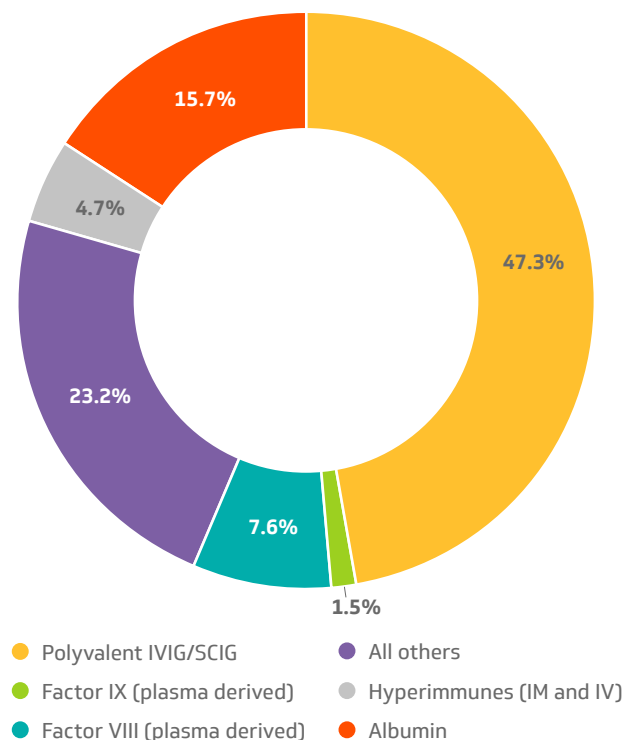
- **IG** — Treats primary and secondary immunodeficiency disorders, viral and bacterial infections, and a growing range of neurological and autoimmune diseases.¹
- **Albumin** — Treats trauma, some liver conditions and cardiopulmonary disease, with continual studies as a treatment for stroke, cirrhosis, Alzheimer's disease, malaria and sepsis.¹
- **Coagulation factor concentrates (factor VIII, factor IX and others)** — Stops or prevents bleeding in patients with hemophilia A, hemophilia B, von Willebrand disease and other coagulation-related disorders.¹

In addition to IG, albumin and hematology factor products, plasma is host to a range of lifesaving therapies, from alpha-1 antitrypsin protein to rabies immune globulin and Rh immune globulin. There continues to be a plethora of unknown proteins that the current technology is unable to stabilize through the manufacturing process, and scientific research has yet to determine the role these proteins play within the complex immune dynamic. Through continued research, there may be opportunities for plasma-derived therapies to offer new or additional treatment options to patients.

While plasma yields many related finished products, IG is the driving force behind the increase in demand. Accounting for almost half of the global plasma proteins market in 2016

(Figure 1), the demand for IG has only increased over the past 20 years, leading to unprecedented growth in plasma collection and manufacturing capabilities.²

Figure 1. 2016 worldwide plasma proteins by product (total market \$21 billion)



Source: Plasma economics: How demand for plasma proteins affects plasma fractionation volumes. Marketing Research Bureau website. <https://marketingresearchbureau.com/plasma-industry/plasma-economics-concept-of-plasma-market-driver/>. Accessed November 7, 2019.

Abbreviations: IM = intramuscular; IV = intravenous; IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin.

How IG works

IG therapy's extensive use in primary and secondary immunodeficiencies is recognized as a lifesaving treatment option through its anti-inflammatory and immunomodulating effects as a replacement therapy.⁴ Immunoglobulins are a class of clinically innovative drugs with great potential as therapeutic agents; they offer a treatment option that patients with acute or chronic immune system disorders can tolerate, sometimes over the course of a lifetime. Studies of IG have shown effectiveness in a variety of medical conditions, and can reduce the need for or complement other medications, including immunosuppressants, corticosteroids and biologic drugs, which have a vast array of complicating side effects and adverse drug reactions.^{5,6}

Despite IG's widespread use in the medical field and within scientific research, the mechanism of action is largely a mystery. "IG has properties that deal with disease in ways we don't completely understand," notes Dr. Toby L. Simon, senior medical director, plasma and plasma safety for CSL

Plasma. Although it remains unclear exactly how IG works, researchers have identified a number of plausible mechanisms of action^{7,8}:

- Anti-idiotypic antibody production
- Reduction of complement pathway injuries
- Modulation of Fc-mediated actions
- Pathogenic cytokine, chemokine and apoptosis-inducing molecule neutralization
- Effects on cell migration by modulation of adhesion molecules
- B- and T-cell modulation
- Direct effect on remyelination

None of these possible mechanisms has been identified as the secret to IG's versatility. It is probable that combinations of several different mechanisms are responsible for IG's therapeutic effectiveness.⁷

Approved and off-label uses of IG

To date, the FDA has approved the use of one or more IG products for the following indications⁴:

- Primary immunodeficiency disorders (PIDs)
- Immune, chronic immune and idiopathic thrombocytopenic purpura
- Multifocal motor neuropathy
- B-cell chronic lymphocytic leukemia
- Kawasaki disease
- Chronic inflammatory demyelinating polyneuropathy

In addition to these conditions, clinicians and researchers outside of immunology have shown the efficacy of IG treatment for a broad range of diagnoses, including lupus, multiple sclerosis, myasthenia gravis and many more. Off-label use for these and other conditions can account for 50% to 70% of the IG administered by U.S. providers.^{3,4}



How and where IG is administered

Although intravenous (IV) administration is the most widely used route, advances in the late 1990s produced a form of IG that could be infused subcutaneously. Initially approved by the FDA for the treatment of PIDs, subcutaneous immunoglobulin (SCIG) administration offers providers and patients a useful alternative. New advances in SCIG may provide further benefit and facilitate the subcutaneous (SC)

route through concentrated formulations, a rapid-push technique that allows for decreased administration times and facilitation of bioavailability through hyaluronidase.^{9,10} The route of administration — whether IV or SC — must take into account patient characteristics, as both routes have unique features (Table 1).

Table 1. Differences between IVIG and SCIG administration

IVIG administration	SCIG administration
<ul style="list-style-type: none">• Venous access required• Presence of trained health care professional is necessary• Compliance is easier to monitor with provider administration• Large infusion volume may result in less frequent dosing• High peaks on initial infusion can lead to an increase in side effects and lower troughs toward end of dosing cycle	<ul style="list-style-type: none">• Venous access not required• Patient may self-administer (after completion of training)• Compliance variable if administered by patient• Multiple needle sticks required• May require more frequent infusions per month• Patients can independently administer therapy• Steady absorption leads to gradual increase in IG serum levels, possibly reducing side effects

Adapted from Berger, Kobrynski and Misbah et al.⁹⁻¹¹

Abbreviations: IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin.

Side effects

Side effects of IG are most often caused by a reaction to a large amount of foreign protein. Systemic side effects are more common with IV infusion, whereas local side effects are more common with SC administration, such as inflammation at the injection site. Side effects — including myalgia, chills, chest pain, fatigue, nausea and headache — may occur during and after infusion and may last for several days. SC administration may reduce these systemic side effects; however, the potential for adverse reactions still exists.⁷ Symptoms may be eliminated or reduced through premedications such as antihistamines, acetaminophen or hydration. It may take several infusions for a patient to begin tolerating any regimen and once a regimen is found to be tolerable, changes to the regimen should be avoided. Some

rare but serious adverse events such as hemolysis and thrombotic events may occur with any route of administration, but is more commonly seen at high doses.

The decision to infuse IV or SC is usually made between patients and their providers as they review the dosing regimen. A number of factors must be considered when deciding when and where infusions are completed, such as patient lifestyle, the type of pump utilized, the number of infusions per month and point of access. Because many patients receiving IG therapy may require chronic or lifetime treatment, dosing regimens must be routinely assessed to ensure compliance and effectiveness of treatment.¹²

Site of care

As with the route of administration, the site of care depends largely on patient and provider collaboration for successful treatment within a variety of settings¹³:

- Hospital inpatient or outpatient with prescriber/nurse supervision

- Physician office or clinic with prescriber/nurse supervision
- Free-standing infusion suite with prescriber/nurse supervision
- Home-based infusion with or without nurse supervision

A range of factors guide selection of the most appropriate site of care, including the patient’s medical history and comorbidities, ability to travel, home environment, previous experience with IG, ability to self-administer and adhere to dosing regimens, access to emergency medical services, availability of a caregiver, third-party payer restrictions, financial burden and preference.¹³

Effective therapy encompasses much more than the simple administration of medication. Inpatient or provider supervised care within an outpatient setting or infusion center clinic provides the ability for active monitoring, adverse effects management and on-site clinical intervention. Patients who may prefer care through these infusion settings benefit from expertly trained staff that are readily available to address concerns ranging from financial reimbursement to disease management. Home-based infusions save in overall health care costs, but patients require additional care coordination and provider follow-up to ensure continual therapy effectiveness. Increasingly, clinical management programs for home-based care are at the forefront of patient intervention; these “high-touch” IG programs provide services such as

pre-infusion clinical evaluations, coordination of individualized infusion plans to avoid adverse drug reactions, patient education, regular clinical follow-up with a pharmacist, and consultation on insurance coverage and financial assistance.¹⁴

Advancements in IG therapy have enabled care to be provided in a patient preferred setting such as the home, resulting in an overall cost savings by increasing compliance and decreasing health care costs associated with hospitalizations and disease complications.¹⁵ Providing therapy in the outpatient setting and at alternate sites of care is driving demand for IG through the increase in off-label utilization. Whereas inpatient- and health-system-based facilities are often governed by formulary adherence, alternate care settings may not operate within such constraints. The differences in the way IG is managed between sites of care — in terms of formularies, indications, dosing and protocols — creates a gap in effective supply management throughout the market and must be addressed for the benefit of all stakeholders within the plasma market.

IG production: a six- to nine-month process

To understand the dynamics of IG supply and demand, it’s important to review the complex, time-intensive and highly regulated journey from blood to plasma and finally to IG. Because plasma and its derivatives must be handled

carefully, protected from contamination, cleared of viruses and tested at every stage, IG production can take six to nine months — and longer if manufacturing issues arise.

It starts with blood

Human blood is made up of two main components — blood cells and plasma. Plasma accounts for 55% of blood volume and is 92% water. Suspended in this water are hundreds of proteins and other substances, including IGs.

Albumin is the most abundant of the plasma proteins, accounting for approximately 54% of the total plasma protein content. The second most common plasma proteins are the globulins, classified into three main subgroups — alpha, beta and gamma. The gamma group, produced by specialized leukocytes known as plasma cells, play a key role in immunity. As a whole, globulins make up approximately 38% of total plasma protein.¹⁶

Because plasma contains much more albumin than IG and other proteins, the efficiency of today’s manufacturing processes always results in significantly more grams of albumin. This explains the seeming paradox of albumin surpluses in today’s tight IG market.

From vein to vial

There are a number of steps involved in the IG production process:

Step 1

Plasma — the raw material of IG — can be separated from donated whole blood or sourced through plasmapheresis at plasma collection centers. The body normally replenishes plasma quickly — within 48 to 72 hours. FDA regulations^{17, 18} allow plasma donors to give up to twice a week, but not two consecutive days. The American Red Cross allows whole blood donations every 56 days.¹⁹ All plasma-derived products used for the treatment of acute and chronic diseases in the U.S. are sourced from U.S. donors. Each plasma and blood donor must meet eligibility criteria and is screened prior to donation to enhance the safety of each lot of pooled plasma. Donors are required to pass examinations and serologic testing on a routine basis and do not become qualified donors until two successful donations of plasma are completed at a plasma collection center.²⁰ “We don’t use the donations of first donors, whom we call applicant donors. It’s a requirement that we have two sets of acceptable screenings and acceptable viral markers on a donor so their product can go into manufacturing,” Simon states.

Step 2

Before plasma is released for processing, it’s held by manufacturers for 60 days. Put into effect in response to the HIV and hepatitis C epidemics, and recently codified into the Code of Federal Regulations, this required hold enables manufacturers to conduct further testing to remove any units that may test positive for infection after the plasma has been collected.¹⁸ “A sample is taken from each donation that’s then tested for HIV, hepatitis B and C, hepatitis A and parvo b19 virus,” says Simon. “Those are the main safeguards in terms of recipient safety. Those are done on each and every donation. Then when all of the plasma is pooled for manufacturing, the pool is also tested.” These additional precautions on behalf of patient safety take time and result in a wait time of approximately 60 to 90 days before the donor’s collected unit goes into full production.

Step 3

After the hold period and pooling of collected units, the plasma is ready for the two- to four-month process of fractionation (Figure 2). The Cohn process, also known as cold ethanol fractionation, exploits the differences in properties of the various plasma proteins through selective

precipitation by the adjustment of ethanol, salts, pH and temperature. At each stage, certain proteins are precipitated out of the solution using a specific manufacturing process for each one. The final precipitate is purified albumin.²¹

Each precipitate continues through additional purification processes such as caprylic acid precipitation and various forms of chromatography. This isolates specific proteins and removes unwanted plasma components — such as anti-A and anti-B — to reduce the risk of hemolysis due to the infusion of ABO-incompatible plasma-derived products. Viral inactivation or viral filtration, which is required to reduce the transmission of bloodborne pathogens, completes the process prior to formulation and vial filling with the final product.²²

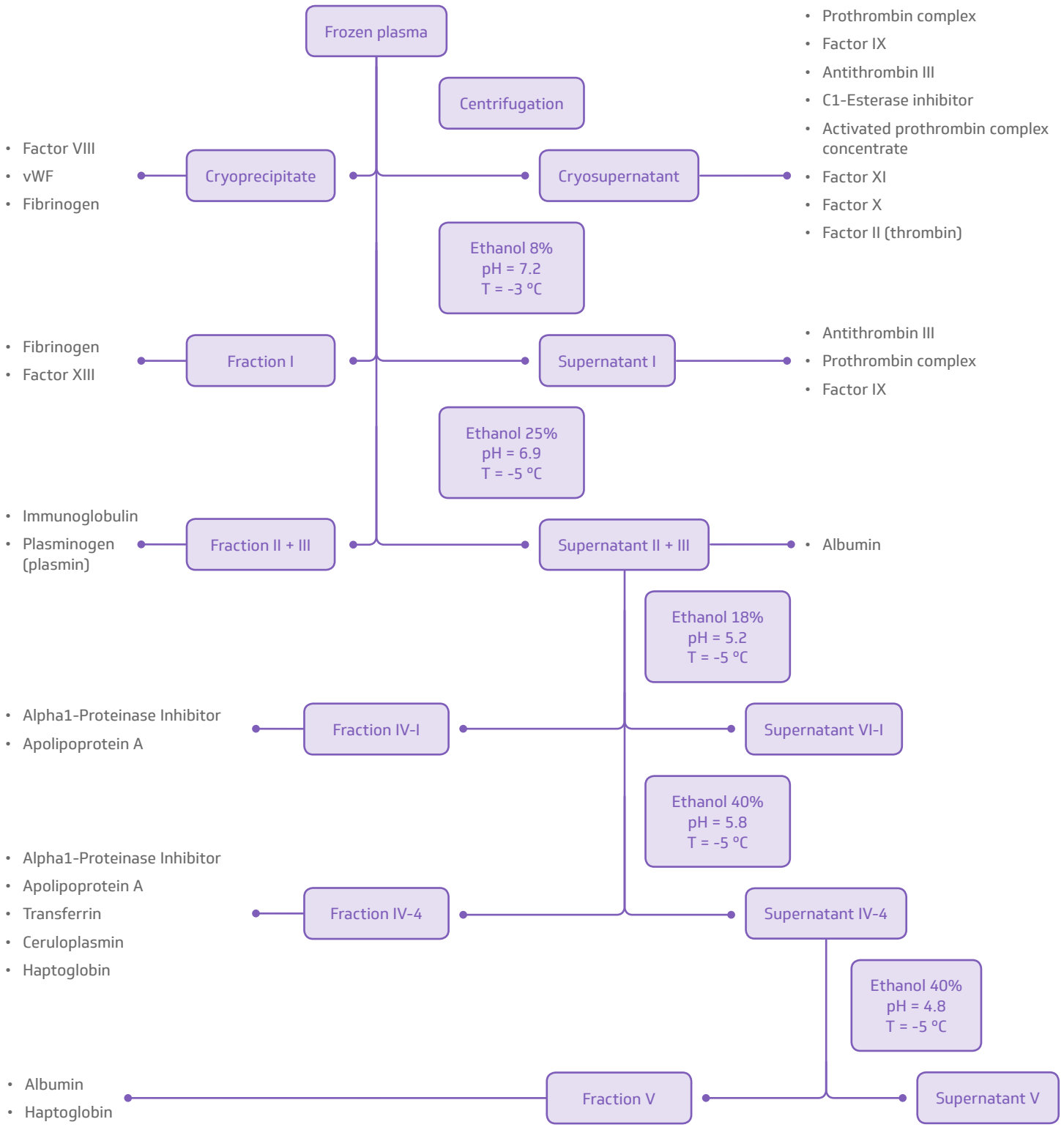
Although most manufacturers follow a variation of the Cohn process, the advancements developed in plasma fractionation and purification to yield the final product have produced patented manufacturing technologies. It’s these patented manufacturing steps that lend each IG product its clinical and brand identity.

Step 4

Upon completion of vial filling, the finished products undergo two to four weeks of rigorous quality reviews. This may include the review of manufacturing records, lot tracing of donated units and FDA approvals. Before the final product can be released into the supply chain, every vial must meet stringent U.S. and international requirements and voluntary industry standards.¹⁸ From there, products are divided into groups by designated destination.

The entire process requires six to nine months from the time the plasma is donated to product completion, with extended time needed for transportation, distribution, and additional quality or regulatory reviews, if required. Because the plasma industry is a global market effort, manufacturing facilities may be located outside the U.S.; however, FDA regulations stipulate that only plasma donated in the U.S. may be utilized for U.S. final product. The FDA approves and certifies international manufacturing sites that will use U.S.-sourced plasma. These international sites add to the logistical implications taken into account during the approval and certification process, and when bringing the finished product to market.

Figure 2. Cohn fractionation process



Source: Bertolini J. The purification of plasma proteins for therapeutic use. In: Simon TL, McCullough J, Snyder EL, Solheim BG, Strauss RG, eds. *Rossi's Principles of Transfusion Medicine*. 5th ed. Hoboken, NJ: John Wiley & Sons, Ltd.; 2016:302-320.

Understanding the current market

Given the complex nature of plasma manufacturing, supply has been unable to meet provider demands, creating a shortage of available product amid a time of increased utilization.

The current supply shortfall began rippling through the market in the fall of 2018. How severe it is — or whether it exists at all — depends on perspective. The term “increased demand” is used nearly as frequently as “shortage.”

“When supplies don’t arrive as expected, and our clinicians aren’t able to access products for their patients — that meets our definition of a shortage.”

Erin R. Fox

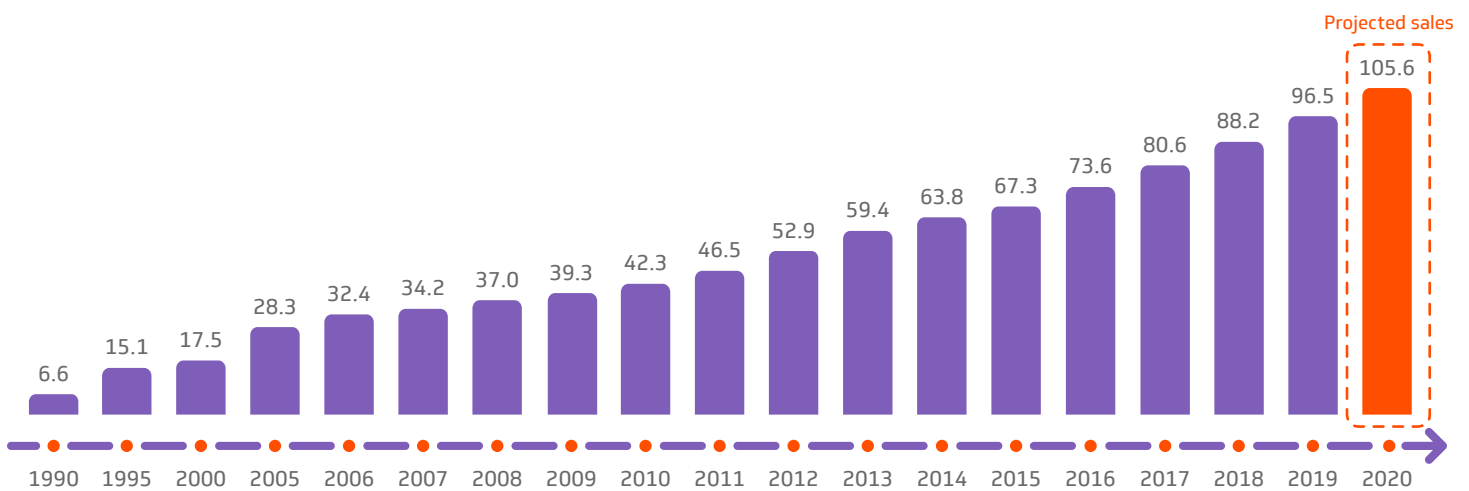
Senior Director, Drug Information and Support Services
University of Utah Health

The pressures of worldwide demand

The global plasma proteins market has reached over \$21 billion, with growth driven by IG sales that represented 47% of the market in 2016. This growth has steadily increased from about 20% in 1984, to 24% in 1996 and 46% in 2008. The rise in IG demand is attributable to the significant technology enhancements in IV and SC administration beginning in the 1980s, along with the prevalence of secondary immunodeficiencies, growing geriatric populations, the surge in off-label use, increased utilization in the outpatient space and increased public health awareness.^{23,24} Within the U.S., IG was valued at nearly \$9 billion in 2017 and is projected to approach \$16 billion by 2025 — a compound annual growth rate of 7.5% from 2018 to 2025.²⁵

In 2015, approximately 67 million IG grams were sold in the U.S. (Figure 3). Given the average annual sales growth of 10% since 2010, it is estimated that over 100 million grams will be sold in the U.S. in 2020. The U.S., United Kingdom and Sweden have the highest per capita IG use — all with more than 200 grams per 1,000 residents. Use varies widely among other developed countries, with Japan, Germany, South Korea and Australia ranging between 75 to 200 grams per 1,000 residents. IG prescribing rates are significantly lower in Brazil, Malaysia, China and India, with clinical use less than 75 grams per 1,000 residents, although adoption is expected to increase as disposable income rises and governments seek to improve the overall population health status.^{26,27}

Figure 3. U.S. sales of IVIG and SCIG, 1990-2019 (grams in millions)



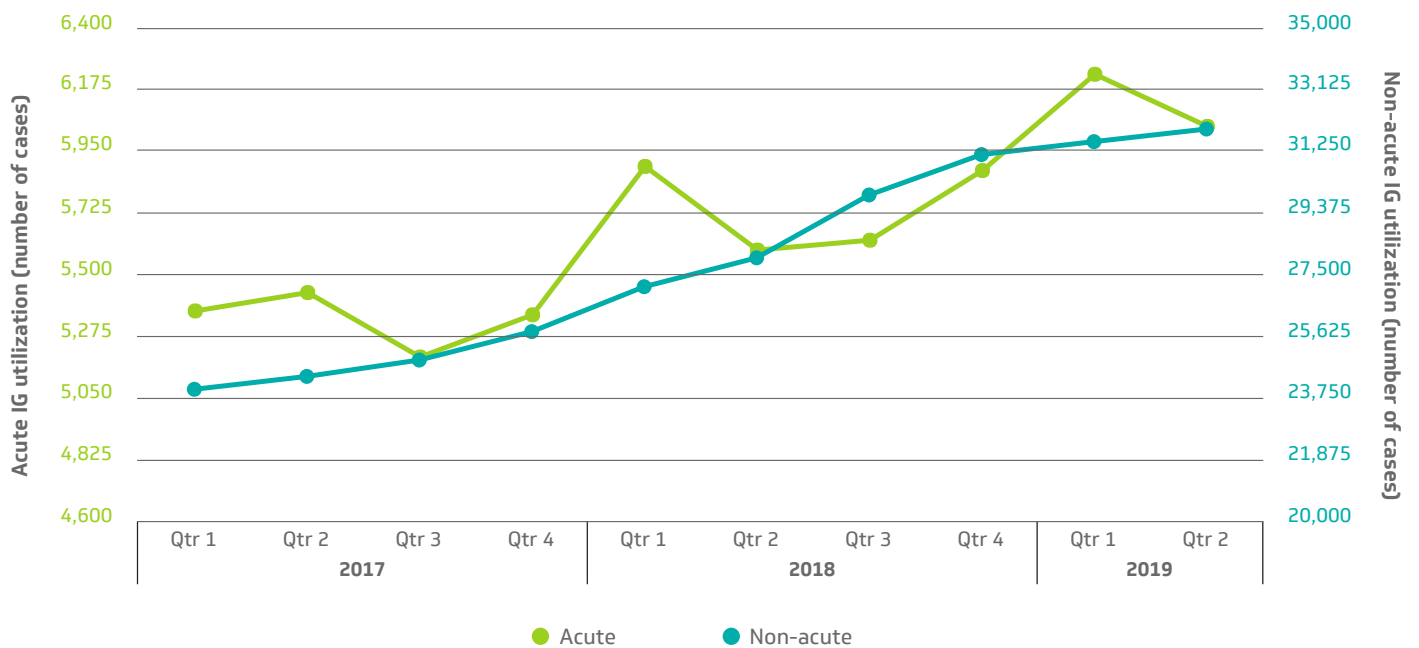
Source: Berman K. Going up: What’s behind the growth in IVIG demand. BioSupply Trends Quarterly website. http://www.bstquarterly.com/Assets/downloads/BSTQ/Articles/BSTQ_2017-01_AR_Going-Up-What's-Behind-the-Growth-in-IVIG-Demand.pdf. Published 2017. Accessed November 7, 2019.

Abbreviations: IVIG = intravenous immunoglobulin; SCIG = subcutaneous immunoglobulin.

Within a subset of Vizient Pharmacy Program participants, utilization as reported by number of cases from various indications continues to trend upwards, despite tightened supply beginning the second half of 2018 and into 2019. While supply affected acute care utilization in the second quarter of 2019 (Figure 4), overall demand continued to drive use in both the acute and non-acute settings when compared to the first quarter of 2018, despite the supply shortfall. Projections for 2019 utilization indicate a 6.8% increase from 2018 for acute care and a 9.2% increase for the non-acute care setting.

During 2017 and 2018, Vizient acute care IG utilization was noted in 594 unique MS-DRG codes submitted for a broad range of disorders.

Figure 4. Acute and non-acute IG utilization, 2017-2019



Source: Vizient Clinical Data Base, 2017-2019.
Abbreviation: IG = immunoglobulin.



Industry challenges in supplying the world

The IG industry consists of a handful of major manufacturers. Because many of their product applications overlap, competition among participants centers on incremental differences in efficacy, clinical formulations, and the ability to research and bring new compounds to market.²³ Increasing the number of manufacturers seems like a logical solution to meet IVIG demand — but the barriers to entry are high, including major outlays for high-tech processing equipment and a dearth in knowledge and experience. As new manufacturers enter the global and U.S. market, the question becomes how much product can manufacturers contribute to the overall market, and will it be enough to close the demand and supply gap.

- On average, plasma donors give **0.8 liter** per visit.
- One liter of plasma yields **4 grams** of IVIG.
- One year of PID therapy for one patient requires **130 donations**.²⁸⁻³⁰

An oft-cited cause of the current tight market is a shortage of recovered plasma (whole blood donations) and source plasma, (paid donations via plasmapheresis). Plasma manufacturing is dependent on plasma donations, with strict regulations on donor requirements. The vast majority of plasma collected is from source plasma within plasma collection centers operated by plasma manufacturers. The U.S. has been the main supplier of source plasma, exporting \$20 billion in plasma a year³¹ by providing up to 71% of source plasma collected globally and 64% of all plasma for fractionation worldwide.

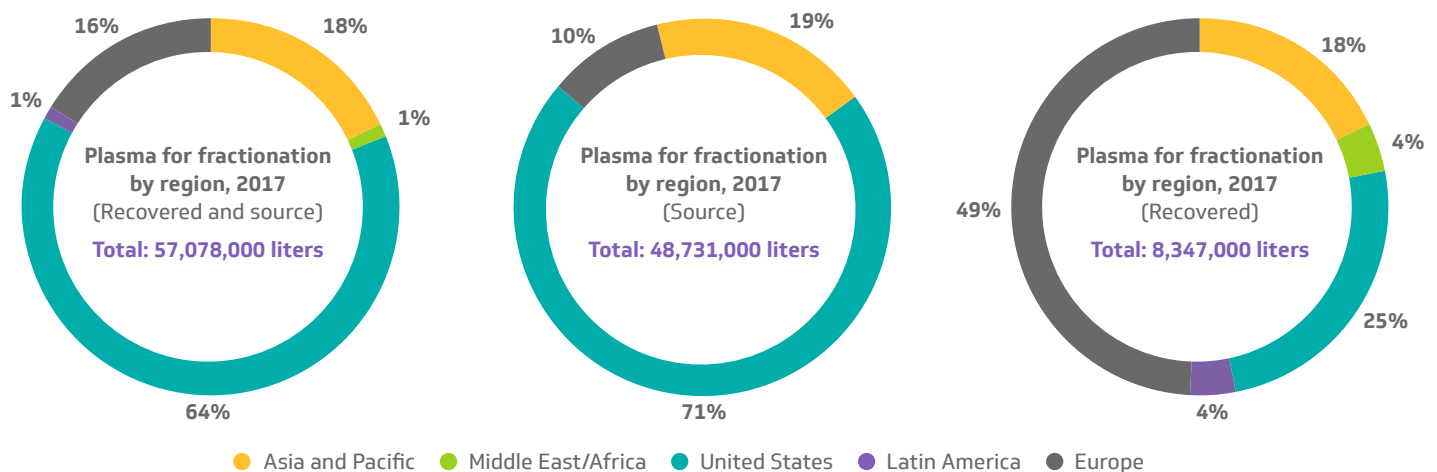
This amounts to a total of 57.1 million liters — both recovered and sourced — reported in 2017 (Figure 5).³²

Even with this substantial collection, there remain significant hurdles to achieving and maintaining sufficient plasma supplies. The U.S. and a handful of other countries play this outsized role because they allow plasma donations from paid donors.³³ Citing multiple concerns, including safety and potential victimization of the poor, the World Health Organization, the Council of Europe and most global regulatory authorities call for national blood systems based on voluntary unpaid donations.¹⁸ However, voluntary donations aren't enough for countries to achieve self-sufficiency. While source plasma accounted for 48.7 million liters of plasma available for fractionation in 2017, recovered plasma for fractionation accounted for 8.3 million liters, with Europe contributing 49% of the total and the U.S. supplying 25%.³²

“Recovered plasma has been diminishing in supply due to the decrease in blood in the form of red cells being used in hospitals,” states Simon. “Therefore, less whole blood is being drawn by blood centers in both the U.S. and in Europe. We have vigorous programs in place to obtain as much plasma derived from whole blood as we can.”

With the diminishing supply of recovered plasma, U.S. manufacturers have concentrated efforts on increasing plasma collection centers through collaboration with local, state and federal regulators. Although the number of domestic plasma donation and collection centers has more than doubled within the last decade — from 349 in 2007 to over 650 in 2017^{27,34} — it's unclear how long the U.S. can meet its own needs and continue to be plasma purveyor to

Figure 5. Recovered and sourced plasma for fractionation by region, 2017



Source: The Source. PPTA website. <https://www.pptaglobal.org/media-and-information/the-source>. Published 2019. Accessed November 7, 2019.

the world. While U.S. plasma is accepted virtually everywhere, FDA regulations require that all IVIG and other plasma-derived medicinal products used in the U.S. be made from plasma drawn at FDA-licensed facilities. At present, these exist only within our borders.

There has been a call within the European Union to allow more flexible guidelines along with increased advocacy efforts within the U.S. itself to increase plasma collection

— and opinions are beginning to change. For example, in May 2018, *The Economist* published an editorial calling for the lifting of bans on paying for plasma, stating that the “limited medical and social risks are dwarfed by the benefits.”³³ There continue to be great socioeconomic debates on the topic, and increasing plasma collection for rare, chronic and critical disease treatment options must be carefully weighed against the incentives offered for the recruitment and retention of plasma donors.

The impact of specialty distribution

Products requiring distribution through the specialty channel — such as IG — comprise high-cost prescription medications used to treat complex, chronic conditions or rare diseases. They often include provider-administered infused drugs and patient-administered oral or injectable drugs. These products are typically biologic in nature and are characterized by:

- Specialty handling, storage and delivery requirements and unique distribution management³⁵

- Significant side effects or risk profiles
- A high degree of ongoing patient assessment or management

Like other complex and costly pharmaceuticals for targeted and rare diseases, IG is distributed through specialty product distributors instead of full-line wholesale distribution.

Why specialty distribution is preferred

Specialty distribution is an important aspect of the commercialization success of IG products. Due to the specific dosing needs of individual patients and the personalized approach they require, traditional pick, pack and ship methods have given way to more immediate just-in-time inventory models. Because these products often require special handling, such as refrigeration, specialty distributors play a critical role in the safe and efficient delivery of these complex medications.

A key factor in the specialty distribution process is its impact on patients. Often, a patient will require infusible therapy for life, which requires support by the caregiver and provider, as well as the specialty distributor. Financial aid for these expensive therapies, nursing and in-home assistance, and psychological-social support for families and patients who face many years of treatments are all critical. Specialty distributors often have patient support services, including financial assistance, reimbursement support and even clinical nurse and case management services.

Specialty pharmaceuticals are often infused in the physician’s office. In these cases, the physician is typically the upfront purchaser of the product, and expects reimbursement from the payer. Specialty distributors will support the physician’s practice or clinic with prior authorization requirements and reimbursement services, as well as payer denials and appeals.

For specialty distributors, hospitals and health systems are becoming an increasingly important customer. For example, due to market pressures, more health systems are expanding into non-acute outpatient facilities and specialty pharmacies, with payer reimbursement — rather than traditional payments — becoming more prevalent. Specialty distributors can support hospitals and health systems with product access and reimbursement support.

“The whole goal has to be to manage and to make sure the maximum number of patients get access to IVIG.”

Patrick M. Schmidt
CEO, FFF Enterprises

Distributors and the art of allocation

In a short and unstable market, specialty distributors play a vital role in determining the types and quantities of IG available for patients in hospitals, clinics and physicians' offices. They use proprietary allocation methods that can vary widely from distributor to distributor.

Some distributors use a straight percentage allocation: If they receive 85% of their expected product from a manufacturer, each customer receives 85% of what they've asked for. Some separate monthly allocations into weekly allotments to control outflow. In other cases, distributors are bound by manufacturer-specified classes of trade or are required to give 100% of their allocations to committed customers first — with any remaining product available afterward dispersed to providers without contracts.

Specialty distributors must understand these nuances. Some take a black-and-white approach to allocation — what you get is based on what you've ordered in the past. Other specialty distributors take a current, holistic view of the market and try to stretch the current accessible inventory of IG grams based on existing need, not just historical purchases.

"We treat the most immediate needs of the patient," says Patrick M. Schmidt, CEO of FFF Enterprises. "If we ship smaller quantities to a facility two or three times a month, it actually costs us more money. But our 31 years of experience have shown that more patients are getting access that week, and maybe the next week, than they would have if we would have just done a percentage allocation based on what we received from the manufacturer."

So where's the art in allocation? It's in the balance of history and current need. It also hinges on health care providers trusting that the specialty distributor is dedicated to helping more patients by stretching the grams of product further over a specific amount of time, while continuing to meet the needs of all customers. "The only way that we built that trust is by years and years of being able to perform in these types of situations," says Schmidt.

For manufacturers, suppliers and providers, working through these issues can be challenging. But the goal is clear: to stretch limited supplies of IG across as many facilities and patients as possible.

Insight into inventory

Visibility into the current inventory is often difficult for the distributor once the product is on-site in the pharmacy, physician's office or clinic. Specialty distributors continue to look for new approaches and technologies to help with this visibility.

Consignment programs are a common approach to tracking and managing some of the higher-cost or less-used inventory. Through consignment, distributors own the product, and stock the refrigerator and shelves. They will also track product expiration dates and replenish the product supply six to eight months prior to expiration. In

this scenario, the customer does not pay for the product until it is removed from the shelf and dispensed to the patient. While the distributor takes on more upfront risk, there is more visibility into the product at the time it is dispensed.

While this inventory control works for certain high-cost, low-utilization products, can aspects of this model be applied to the management of IG? As distributors review various model concepts for inventory transparency, providers need to weigh the benefits of distributor versus provider inventory control.

Manufacturer controls of distribution partners

Because of the smaller production output and the volatile nature of demand, manufacturers also play a big role in determining product allocation, as well as classes of trade in which the product is distributed, often putting pressure on their specialty distribution partners.

For example, one large plasma manufacturer manages a committed customer program that includes more than 50 non-acute customers, and requires these committed customers to be the first to receive product. In the same spirit, another manufacturer requires the allocation of its grams to be dispersed to seven customers through five distributors.

Another complication is the demand for albumin. Non-acute facilities typically do not have a need to purchase albumin, while acute facilities use IG, albumin and factor products. Some manufacturers use this opportunity to drive albumin purchases.

All of these nuances require a specialty distributor that has a deep knowledge of the industry and trusted relationships with manufacturers — and the ability to manage the two.

The role of payers and reimbursement

IG accounts for the third greatest drug spend in commercial plans and the fourth under Medicare — despite the fact that less than 1% of the covered population needs it.

Payers use a variety of methods to ensure that IG is used for the right patient in the right setting. By far the most prevalent is prior authorization (PA). A recent study indicated it is used by 88% of commercial payers (Table 2).¹³

Varying greatly from plan to plan, the PA process restricts the use of IG to certain specialties for specific indications or specific brands. As shown in Table 2, other management tools include site-of-care programs, education for providers and patients on the possibility of switching from IVIG to SCIG, shifting coverage from the medical to the pharmacy benefit and formulary restrictions.¹³

Table 2. 2016 utilization management tools for IVIG and SCIG

	Commercial (percentage of payers; n = 49) 109 million covered lives		Medicare Advantage (percentage of payers; n = 8) 32 million covered lives	
	IVIG (%)	SCIG (%)	IVIG (%)	SCIG (%)
Care management	24	16	25	13
Clinical pathways	8	4	0	0
Differential provider reimbursement by drug in therapy class	4	0	NA	NA
Dose optimization	16	8	NA	NA
Patient adherence program	4	4	NA	NA
Post service claim edits	14	12	13	13
Prior authorization	88	84	75	75
Site of service	22	12	13	13
Step-edit requirements	6	4	NA	NA
None	2	14	25	25
Other	4	2	NA	NA

Source: Vaughan L. Managing cost of care and healthcare utilization using immunoglobulin agents. AJMC.com website. <https://www.ajmc.com/journals/supplement/2019/examining-the-application-immunoglobulin/managing-cost-of-care-and-healthcare-utilization-in-patients-using-immunoglobulin-agents?p=3>. Published June 28, 2019. Accessed November 7, 2019.

Abbreviations: IVIG = intravenous immunoglobulin; NA = not available; SCIG = subcutaneous immunoglobulin.

While the goal for utilization management programs has been to decrease the cost of care across the health care continuum, the complexities of reimbursement and varying management strategies in terms of how care is administered can complicate business operations. Switching patients from IVIG to SCIG involves patient and provider coordination to ensure the patient is a candidate for a change that often encompasses much more than route of administration. Some health plans adjust benefit designs to shift coverage of IG from a medical to a pharmacy benefit, which requires adjusted billing practices and coordination with various specialty pharmacies to obtain medications and remain compliant with the preferred formulary strategies of the pharmacy benefit manager.¹³

The need for payer restrictions is a result of an overwhelming array of medical conditions. With an average annual expense of approximately \$30,000 to \$90,000 per patient depending on dose, infusion time, length of treatment and site of care,³⁵ managed care organizations have implemented various strategies to promote the judicious use of IG replacement therapy. In general, private insurers align with Medicare and reimburse for all FDA-approved IG indications. In addition, many cover a significant number of common off-label uses that are supported by outcomes data or clinical research.

A study published in 2014 across six health plans found that of the 2,548 managed care PA requests for IG therapy received between February 2008 and August 2012, a total of 181 unique indications were identified. The level of evidence for PA requests was reviewed and 57.6% were found to be supported in relevant literature (i.e., medical conditions for which IG treatment is supported in consensus papers as first-line or for FDA-approved indications). The remaining 42.4% of PA requests were designated as conditional, lacking consensus, currently not supported or undetermined (Table 3). For all evidence levels, the approval rate of benefit coverage was 82.2%.³⁵

Payer guidelines not only delineate the specific indications that IG treats, but also the preferred site of care, since IG is generally considered more economically feasible for both patients and providers in select outpatient settings. “Limit the network, limit the products on formulary and limit the site of care. That might mean a shift from the hospital outpatient site of care — the most expensive care setting — into the ambulatory infusion centers or home infusion,” states Schmidt.

To assess this more economical treatment option, the Centers for Medicare & Medicaid Services (CMS) was mandated to evaluate bundled payments through the Strengthening Medicare and Repaying Taxpayers Act of 2011, and determine whether introducing a bundled payment for items and services associated with home administration of IVIG improved access to care for beneficiaries with primary immune deficiency disease. CMS found that from January 2013 to March 2018, clinics (including physicians’ offices) and home health care increased in overall market share by channel, representing the majority of IG product sales; conversely, nonfederal hospitals represented the highest decline (Figure 6).³⁶

Driven by reimbursement and the expense of the hospital outpatient setting, payers have created site-of-care programs to incentivize patients to choose settings such as home infusion or ambulatory infusion centers. A survey of 59 commercial health plans representing over 76 million covered lives found that 89% had an IVIG-specific site-of-care program. In addition, the survey found that health plans using site-of-care programs increased by 135% between 2013 and 2017.¹³ One study found that alternative outpatient settings such as home infusion have been shown to increase compliance among patients receiving IVIG infusions while simultaneously lowering the cost per infusion up to 31% when compared to an outpatient hospital setting, with an overall annual savings of \$18,876 to \$26,136 for each patient receiving 13 to 18 infusions per year.³⁷

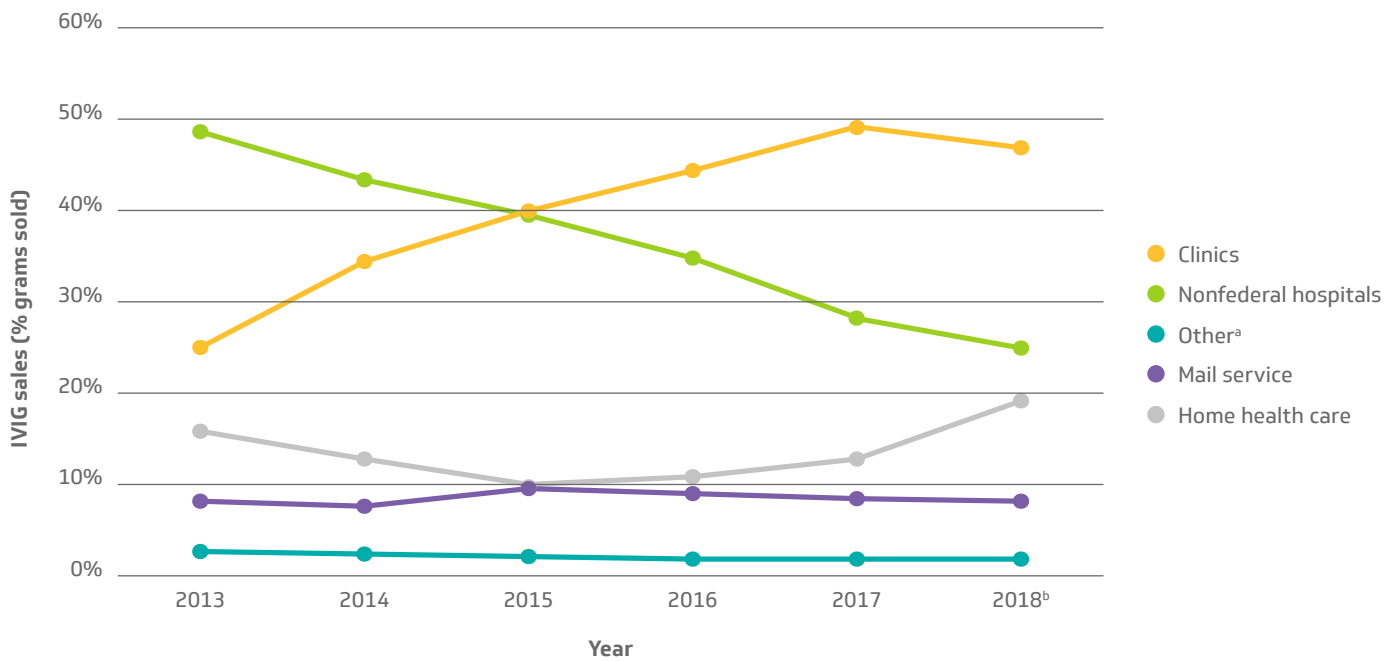
While it may be necessary to promote the effective use of these high-cost products, there are certain scenarios where these limitations can create a delay in the provision of care. While restricted formularies and fail-first policies are important utilization management strategies, payers must balance limited product reimbursement with the increased risk of adverse events.¹³ Limiting where the patient can receive IG through site-of-care programs may place additional travel burden on the patient, especially in rural areas. Formulary restrictions on IG brands create barriers to access, particularly in a lean market. This has made the provision of patient care challenging, as IG products are not generally interchangeable and a specific IG should be matched to patient characteristics to ensure safety.³⁸ Thus, providers unable to obtain certain products preferred on formulary under any one payer are either unable to treat the patient or face the difficult decision of switching therapies. “If the payer is adamant that we use a particular brand and it’s not something we’re getting or have access to, we would have to decline the referral,” says Karmen Stowe, purchasing manager, American Outcomes Management. “At this time in this market, we get what we can and we have to make it work.”

Table 3. Evidence levels by benefit coverage outcome

Evidence level	Health plan benefits authorized (n)	Health plan benefits denied (n)	Total
Supported	1,272	195	1,467
Conditional	696	134	830
Lacking consensus	62	65	127
Currently not supported	30	44	74
Undetermined	34	16	50
Total	2,094	454	2,548

Source: Tonkovic B, Rutishauser LK. Descriptive review and analysis of immunoglobulin utilization management from 2,548 prior authorization requests. *J Manag Care Spec Pharm.* 2014;20(4):357-367.

Figure 6. IVIG sales by channel, 2013-2018



^a The “Other” category includes federal facilities, chain stores, food stores, HMOs, long-term care facilities and miscellaneous other establishments.

^b 2018 data only through Q1.

Source: U.S. Department of Health and Human Services. Update on supply of immune globulin intravenous (IGIV) products. Office of the Assistant Secretary for Planning and Evaluation website. https://aspe.hhs.gov/system/files/pdf/261751/IGIV_Market_Update.pdf. Published May 2019. Accessed November 7, 2019.

Abbreviations: HMO = health maintenance organization; IVIG = intravenous immunoglobulin.

In order to induce payers to cover reimbursement for products not on formulary, providers are increasingly being required to submit letters referencing information from the FDA or the American Society of Health-System Pharmacists^{39,40} that indicate that products are in short supply. Coupled with the increased number of PAs, providers are shouldering a heavy administrative burden. “Even with the appeal process, we still have to conduct peer-to-peer reviews and have the physician call in. Most of the time it works, but sometimes it doesn’t,” states Stowe.

Consequently, dealing with restrictions can require significant administrative time and delay the start of treatment. A Vizient member survey found that U.S. hospitals spent \$359 million in annualized labor costs to manage drug shortages, equating to an additional 8.6 million labor hours. These costs of care are an added burden to health care systems navigating an already complex supply market.



How health care organizations are responding

As manufacturers work to increase plasma supplies and build IG production capacity, providers and their patients face the life-altering impacts of delayed, compromised or denied treatment. Vizient members report a constellation of concerns, all of which emphasize the need for greater alignment, both upstream and downstream. These challenges include:

- Insufficient information from manufacturers and distributors related to product access, which cripples planning

- Inconsistent product availability and allocation
- Varying degrees of success within the supply chain in stabilizing the available supply
- Delays in treatment uptake, inability to treat and forced product-switching
- Pushback from payers that complicates product choice and flexibility, and access to therapy

Health care organizations are responding to the challenge of a tight IG market in a variety of ways, yet are bound by the need for clarity, standardization and continuity of care.

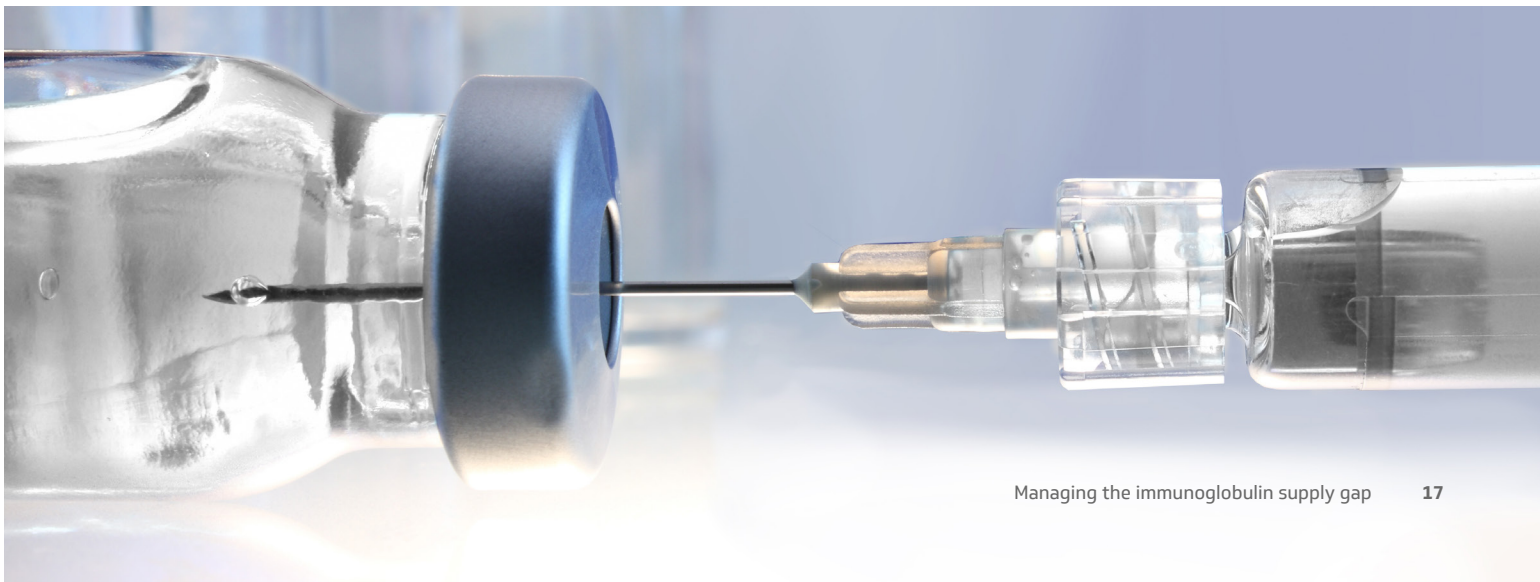
Fostering clear communication

University of Utah Health is managing the current IG shortage through its regular pharmacy and therapeutics committee and medical board, but senior directors Erin R. Fox and Kavish Choudhary stress the importance of keeping everyone affected in the loop. “Our standing shortage protocols include daily huddles and weekly email updates,” Fox notes. “We’ve had to engage with providers, pharmacy buyers, finance, pharmacy technicians, nursing staff, the director of nursing for the infusion centers and schedulers. This is how we’ve made it work, but it hasn’t been easy. Roughly 20 or 30 people are regularly involved,” Choudhary adds.

With the need for transparency top of mind, Matt Wolf, coordinator of pharmacy services for Allina Health, and Stowe have both developed shared IVIG management tools that keep key staff members updated. “Due to the sheer volume and importance of the shortage, sharing and tracking between sites is something we’ve gotten really good at,” Wolf says. “We keep a massive master spreadsheet that provides us with all of our IVIG supply and patient

requirements,” says Stowe. “We do an inventory every day and balance to what we show we should have after everything’s come in and gone out.”

Clear communication is also required between the health system pharmacy and providers about the shortage and its impact on their practices. In its core communications to its providers, Allina explained the crisis and the immediate limitation of IVIG new starts to patients with first-line indications. “We stressed the importance of contacting pharmacy first before initiating new treatment,” Wolf explains. “Knowing in advance enables us to check across the system and make sure we have enough product that month to start a patient on that medication.” Fox and Choudhary use phone calls, text messages, emails and face-to-face conversations with providers. “We let them know that our goal is to make sure we can treat all of our patients — and that we need their help to make it happen,” Choudhary says.



Driving standardization to manage allocation

For Wolf, Allina's IVIG system formulary recommendations are helpful because all 13 hospitals in the system follow them for inpatient and outpatient care. "That unified formulary committee streamlines our ability to approve appropriate use guidelines for first- and second-line indications," explains Wolf. The intervention of approved pharmacists who can make body-weight adjustments instead of automatically filling provider orders has also helped Allina.

Choudhary and Fox drive standardization and allocation efficiencies by instructing manufacturers and distributors to send IVIG shipments to the main hospital. From there, staff allocates supplies to the system's four infusion centers and home infusion group. "Deploying the product has added quite a bit of work for the central pharmacy, but now we know there's no inventory sitting idle in any of our locations," Choudhary explains.

Fox and Choudhary also pushed to make sure the system was following its own dosing guidelines, especially in terms of body weight. "We started making sure we were at the ideal body weight to determine grams," Choudhary says.

Controlling and standardizing indications also optimizes the allocation of grams. In essence, the shortage has forced a tougher stance on how IVIG is used. "We've had pretty strict criteria for several years," Choudhary says. "We start with what's payable by Medicare and, in the outpatient setting, add indications the patient's insurer will cover." What's obsolete are inpatient uses where the potential benefits are untested or unknown. "Our providers set the precedent," he notes. "If IVIG isn't going to improve things, let's save those 80 grams for patients who can truly benefit."

Managing continuity of care: another key allocation strategy

As health systems tighten IG guidelines, everyone across the care continuum needs to be aligned. On the acute side, systems have more experience reining in off-label creep and prioritizing the acute patients who need treatment most. "We started having discussions about whether we needed to divide patients into first-line or second first-line indications, or whether it was time to involve our ethics committee," says Wolf, referring to the critical decisions health systems make to ensure the appropriate treatment of their patients. Supply managers and providers who are ordering and administering IVIG in outpatient settings have to consider the implications to market supply and dynamics and utilize IG for the patients who will benefit from treatment — even when off-label uses are approved for payer reimbursement.

Fox and Choudhary underscore the importance of confirming coverage as a key step in the management of IVIG allocation, especially when outpatient IVIG therapy is anticipated to follow acute inpatient care. Citing the example of a bone-marrow transplant patient with hypogammaglobinemia, Fox explains that even as inpatient care for this approved indication is being arranged, case managers are working closely with the insurer to secure

pre-authorization for the follow-up outpatient phase. "We don't want to start a therapy the patient may not be able to continue," she says.

For chronic patients, regular testing can help determine when it's safe to skip or delay an IVIG treatment. Disease remission also allows for tapering of treatment. "Working with providers, we looked at reducing doses and extending intervals," Utah Health's Choudhary explains. "For patients with strong test results who are feeling good, it's OK to push things out a week or two."

Finally, when a life-changing therapy is in short supply, providers need to confirm that the IG therapy is being applied where it can actually make a difference. One study published in 2018 showed that only 32.2% of 248 patients had an immune neuropathy and were appropriate candidates for IVIG therapy, while 15.3% of cases met electrodiagnostic criteria for a demyelinating neuropathy.⁴¹ The overall treatment response rate was found to be 36.7%.⁴¹ While diagnosis and treatment for patients can be an art requiring skill, experience and intuition by the clinician, it's important for providers to focus on getting IG to the patients who are correctly diagnosed and will respond to the therapy.

Toward a long-term solution

In a market where all participants share the mission of helping the greatest number of clinically appropriate patients receive IG treatment, there's a unifying desire for collaboration and transparency. As John G. Boyle, president and CEO of the Immune Deficiency Foundation, wrote in a July 2019 article:

“Neither IDF, the FDA, the Plasma Protein Therapeutics Association nor anyone else engaged in this can do it alone. We need each other. Until we again reach a point when the supply of IG and other plasma products allows everyone more breathing room — we need your attention, your understanding and your collaboration so we can halt this troubling trend and foster responsible stewardship of IG as a vital therapeutic resource.”⁴²

Transparency is key to the successful management of IG, where all parties — manufacturers, distributors and providers — can contribute by managing the flow of product through the supply chain to patients. Only then can each stakeholder participate in addressing the demand we are facing within this market. With repercussions that reverberate to the patient and community, the importance of being good stewards regarding the judicious manufacturing, distribution and use of plasma-derived therapies starts with an open culture of information sharing and cooperation to achieve the best strategic results.

Manufacturers

Transparency starts with a trusting partnership with our manufacturers and suppliers. Providers looking to the key contributors of plasma-derived therapies for direction underscores the necessity for open dialogue. The current supply challenges highlight the importance of communicating how the manufacturing process and its regulations affect the forecast and economics on an individual provider level, as well as actions manufacturers are taking to address key issues affecting supply. Open communication needs to trickle through all levels of the

supply chain — from manufacturer to distributor, both of whom need accurate and timely information to service the providers, to the patients, who need to understand how supply may affect their therapy choice.

As a voice of advocacy, Vizient, in collaboration with our supplier partners, can bring together critical resources to educate and help providers navigate the complex plasma market while enabling economically viable accessibility to plasma-derived therapies.

Distributors

Distributors play a key role in increasing transparency across the market by connecting providers to products. For providers to operate effectively and efficiently, accurate communication is expected with regard to shipment quantity, product specificity and frequency. When the distribution process becomes unpredictable, patient care and provider forecasting is adversely affected. Transparent communication is vital as providers balance inventory and patient care. “We are managing our product to the gram every day. As we bring patients on we have to look at our current inventory, anticipated deliveries from distributors,

our expected shipments out to the patients and changes in patients’ orders,” says Stowe. Together with distributors, Vizient and providers must collaborate to provide the support required for patients and manufacturing partners through transparent, accurate and timely analytic feedback, which ensures the consistency of the distribution supply chain. To that end, the Vizient analytics platforms are critical to identifying opportunities for providers while pinpointing patterns — both consistent and inconsistent — across the supply chain.

Providers

Providers are crucial to this patient care community, and serve as the main driver in our advocacy for greater transparency and accountability. Providers also help to foster a culture of education and promote the judicious use of plasma products. Plasma collected from donors is a limited resource, yet provides the basis for the lifesaving therapies patients depend upon. As stewards of these therapies, it's incumbent upon providers to use only what is necessary and institute guiding principles for safe, appropriate and effective use. Establishing stewardship

programs is critical and should extend beyond mitigation strategies and evidence-based protocols. Through interdisciplinary collaboration, providers can bring about the transparent coordination of care by establishing reimbursement processes, informatics protocols, accurate accounting and tracing, and utilization forecasts. Education is the first step in this therapy arena, and through Vizient resources and collaboration networks, providers can realize their potential in positively impacting quality and cost-effective care.

Conclusion

Today's IG shortage encompasses intricacies that stretch around the globe and into the heart of every community. Fundamentally, the issue is one of supply and demand. More parts of the world are seeking the miracle of IG for their populations, and more conditions are coming under its sway.

The need for plasma and plasma-derived therapies grows each year, and the complex nature of IG products as biologics means that it takes time to increase the supply. Clinicians and research continue to find increasing value in the immunomodulatory capabilities of IG therapy, creating unprecedented growth in demand. Meeting the demand first requires more plasma — a priceless raw material that

more people must be convinced to donate. Next, the industry must greatly expand manufacturing capacity to transform it into usable treatments. Finally, distributors must adopt methods that enable providers to plan for and deliver optimal patient care. Active cooperation is needed from all parties to ensure the efficient flow of safe and effective product use.

Every step in the solution takes time, and no step is guaranteed. In the meantime, greater stewardship, coordination and transparency can help ensure that every gram is used where it's needed most and that no gram is wasted.

About Vizient Pharmacy Solutions

Vizient supports health systems and hospitals in transforming pharmacy from a cost center to a central point of integrated care across acute, non-acute specialty, home infusion and long-term care, through solutions that manage cost, improve quality outcomes and drive organizational performance.

To learn more about the Vizient plasma program, contact pharmacyquestions@vizientinc.com.



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