

# Immune Globulin

## *Controlling Supply and Demand*

While the healthcare industry is currently experiencing an oversupply of the lifesaving immune globulin therapy, with demand growing at 6 percent to 8 percent a year, is it possible another shortage looms large?

By Ronale Tucker Rhodes, MS



In March, the U.S. Government Accountability Office reported that the number of drug shortages has more than doubled since 2007.<sup>1</sup> Shortages of drugs, many of which treat life-threatening diseases, create public health threats and often lead to preventable deaths. In the mid- to late-90s, a major shortage of immune globulin (IG), a human blood product used primarily to treat immunodeficiencies and autoimmune diseases, caused patients to go without treatment and risked their lives. Is it possible that another nationwide shortage of IG looms large? While it is often hard to predict if or when a shortage will occur, understanding what caused a past shortage, where we are now and what steps the industry is taking to help prevent another can help shed some light on the supply and demand of IG in the future.

### A History of Supply and Demand

The IG market is a classic supply-and-demand situation. According to Chris Ground, chief operating officer at FFF Enterprises Inc., a supplier of critical-care biopharmaceuticals, plasma products and vaccines, “When supply is low, we refer to it as a short market, which means demand is higher than supply. When there is ample supply, it is known as a long market, one where demand isn’t keeping pace with supply.” Why a market switches from short to long and back again is primarily a result of current and predicted demand, but there are other reasons as well.

In 1997, then-U.S. Surgeon General David Satcher, MD, PhD, estimated a 20 percent shortage of intravenous IG (IVIG).<sup>2</sup> In 1998, the U.S. Food and Drug Administration (FDA) estimated the shortfall at 30 percent. Manufacturing standards violations and product recalls were the two major reasons for this shortage. FDA attributed approximately 60 percent of the decreased availability to production impediments related to compliance and approximately 20 percent to withdrawals of plasma products.<sup>3</sup> It all began in 1995, when FDA issued recommendations that plasma products made from pools later found to include a donor with a fatal and little-understood disease known as Creutzfeldt-Jakob disease (CJD) be withdrawn from the market. This resulted in both recalls and voluntary withdrawals. By 1997, industry records showed that the four manufacturers that produced the vast majority of IG — Bayer, Baxter Healthcare, Alpha Therapeutic and Centeon — had recalls and withdrawals totaling about 7 percent of the total supply.<sup>4</sup>

The shortage was addressed in two ways. In January 1998, FDA reminded physicians of the six approved uses for IVIG and recommended that priority for the therapy be given to patients who have FDA-approved indications. Then, a review of data from FDA, the National Institutes of Health and the Centers for Disease Control and Prevention suggested that the risk for transmission of classic CJD by blood products, if it

existed, was considerably lower than the risk for harm to public health from CJD-related quarantines and withdrawals. So, in August 1998, the Surgeon General recommended that plasma derivatives, including IVIG, be withdrawn only if the blood donor developed new-variant CJD.<sup>3</sup>

Shortly after the FDA recommendation to withdraw IVIG due to CJD in 1995, FDA doubled its inspections of manufacturers of plasma products and discovered serious violations of manufacturing standards. As a result, every company in the business received warning letters citing numerous deficiencies.<sup>5</sup> Yet, while FDA allowed manufacturers to continue operating while addressing regulatory problems, some companies decided to stop release and distribution of IG and to shift resources to compliance correction. Centeon, in particular, decided to shut down production and didn’t distribute product at all in 1997, accounting for 60 percent of the 20 percent product shortfall.<sup>2</sup>

Unfortunately, while supply was falling, demand was surging. Increased demand was a result of both new approved indications and an increase in off-label (non-FDA-approved) uses of IVIG. Medical studies found IVIG to be effective for treating several neuromuscular and other diseases. The Immune Deficiency Foundation and physicians at major centers estimated 50 percent to 70 percent of the drug was being prescribed for off-label use.<sup>2</sup>

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Export of IVIG was also another factor contributing to the shortage. FDA reported that exports accounted for up to 29 percent of distributed product, depending on the manufacturer. The International Plasma Products Industry Association reported that exports from the major U.S. fractionators increased from 1996 to 1997, accounting for about 20 percent of their marketed IVIG products.<sup>2</sup>

While there has not been a major shortage of IG since this one, there have been concerns. In 2005, the American Society of Health-System Pharmacists (ASHP) reported an impending shortage due to several factors. First, there was consolidation in the blood product industry when Baxter Healthcare and the American Red Cross pulled out of the plasma production market and three other suppliers cut production. In addition, most companies were gearing up to provide liquid preparations in place of their lyophilized powder preparations, which

resulted in a lag time in production while manufacturing practices were changed. And, growing use of IVIG continued at a rate of 5 percent to 10 percent annually, mostly due to new indications.<sup>5</sup>

In 2010, the market experienced a complete withdrawal of Octapharma's Octagam. Even though Octapharma was not one of the top-three producers of IVIG for the U.S., the voluntary withdrawal still affected the U.S. market since supplies from all markets were needed to fill the void of the loss of Octagam from the U.S., Australia and Europe.<sup>6</sup>

### Plasma Collection and Manufacturing

Manufacturers estimate IG usage is growing at 6 percent to 8 percent each year; however, healthcare professionals assert that estimate is too low, and that a more accurate estimate is 10 percent to 15 percent.<sup>7</sup> Either way, an increase in demand for these products first necessitates an increase in the raw product: plasma.

In the United States alone, there were more than 29 million donations of plasma collected in 2013, according to the Plasma Protein Therapeutics Association (PPTA). This is more than double the increase of 12 million donations over the previous decade. Worldwide, the total annual demand for plasma by pharmaceutical companies that manufacture plasma-based therapies is about 38 million liters.<sup>8</sup> Most of the world's plasma is collected in about 400 plasma donation centers scattered throughout the U.S., with some of it exported to other countries. For instance, countries such as those in Europe are unable to pay for donations, which creates a demand for exportation from the U.S. The U.S. Centers (owned exclusively by plasma therapy manufacturers) pay between approximately \$15 and \$40 for a donation of plasma.

Once collected, plasma — 92 percent water and 8 percent proteins — must go through a fractionation process that separates and collects the individual proteins, of which 64 percent are albumin, 20 percent are immune globulin, 2.5 percent are alpha-1 antitrypsin, less than 1 percent are clotting factors, and 13.5 percent are others such as antithrombin, protein C, C1 esterase inhibitor, etc.

As part of the industry's voluntary international standards program for manufacturers, known as the Quality Standards of Excellence, Assurance and Leadership (QSEAL), all plasma is held in inventory for 60 days before it can enter the manufacturing process. This allows for rigorous testing to identify, retrieve and destruct plasma donation from donors who are disqualified for various reasons such as having received a tattoo or piercing at the time of the original donation or failing to report foreign travel.<sup>9</sup> Most recently, due to the outbreak of Ebola, PPTA has endorsed the recommendation by the EU Center for Disease Prevention and Control that travelers or residents returning from Ebola virus disease-affected areas be

deferred for donation of plasma for fractionation two months after return. PPTA says its voluntary inventory hold of all incoming plasma for fractionation of 60 days is adequate to allow for removal of a unit in question if necessary.<sup>10</sup>

Once the plasma is released from inventory, it is ready for fractionation. During the fractionation process, plasma is pooled from multiple donations, purified and processed in a specific order to extract specific plasma proteins that have a proven health benefit. The steps and regulations required to collect donated plasma and complete the manufacturing process that ultimately results in the final therapies takes between seven and nine months. Between weeks 0 and 4, the plasma is collected. Then, between weeks 4 and 12, it is batched and transported to the fractionation plant, where it is stored from weeks 12 through 16. During this period, "it is the combination of time, temperature, pH and alcohol concentration [that] allows the extraction of the specific therapeutic proteins." At that point, the plasma is inspected and released for production. Production occurs between weeks 20 and 24. Then, between weeks 24 and 28, internal testing of the therapeutic proteins takes place, and the therapies are then released by FDA and shipped between weeks 28 and 32 to the wholesalers and end users.<sup>9</sup>

### The Current IG Market

In the U.S., there are currently seven companies — Baxter, Biotest Pharmaceuticals, BPL, CSL Behring, Grifols, Kedrion and Octapharma — that manufacture and market IG products administered intravenously (IVIG) and subcutaneously (SCIG). IVIG products include Carimune NF, Bivigam, Flebogamma 5% DIF, Flebogamma 10% DIF, Gammagard Liquid, Gammagard S/D, Gammaked, Gammalex, Gamunex-C, Octagam 5%, Octagam 10% and Privigen. SCIG products include Gamunex-C, Gammagard Liquid, Gammaked, Hizentra and HYQVIA. The newest entries to market are Bivigam in 2013 and HYQVIA in 2014.

A 15th IVIG product that is expected to enter the market is ADMA Biologics' RI-002. In December, the product demonstrated positive results and successfully achieved its primary endpoint in a Phase III trial in the U.S. for the treatment of primary immunodeficiency (PI). ADMA plans to report on additional secondary endpoints when the data is available, and it is currently assembling its biologics license application for planned submission to FDA during the first half of 2015.<sup>11</sup>

An additional two investigational SCIG products are also undergoing clinical trials. Baxter is in Phase II and III trials for its 20% SCIG to treat patients with PI.<sup>12</sup> Octapharma is scheduled to complete its Phase III clinical trial of Octanorm, a 16.5% SCIG to treat PI patients, in June 2016.<sup>13</sup>

With considerable growth over the past decade in the number

of companies that manufacture IG (from five to seven, and soon to be eight, despite a merger between two previous manufacturers) and the number of IG products (from 10 to 14, and soon to be 17) that are FDA approved to treat only six indications, the supply and demand outlook would appear to be optimistic. (Depending on the product, the six indications include PI, idiopathic thrombocytopenic purpura, multifocal motor neuropathy, chronic lymphocytic leukemia, Kawasaki disease and chronic inflammatory demyelinating polyneuropathy.) But, medical evidence shows IG is beneficial for treating many off-label indications, which, according to past estimates, represent 50 percent to 80 percent of total IG use.<sup>7</sup> These indications include a host of autoimmune disorders such as Guillain Barré syndrome, multiple sclerosis, chronic fatigue syndrome, myasthenia gravis and Sjogren's syndrome that are now being routinely prescribed high doses of IVIG. And, even as the demand for plasma-based therapies continues to increase, several manufacturers are exploring new indications — two major ones being Alzheimer's disease and recurrent miscarriage.

Therefore, as the number of patients needing IG treatment continues to multiply as doctors prescribe IG for off-indicated uses and research expands to determine the effectiveness of IG to treat other conditions, the potential for a shortage heightens.

### **The Industry's Role in Ensuring Supply Meets Demand**

Manufacturers strive to ensure that supply will meet demand. But, predicting how much IG to manufacture is challenging. For one, the fractionation process is lengthy, taking approximately seven to nine months from when an individual donates plasma to when the medication is ready for use. Therefore, says Ground, "manufacturers have to have a seven- to eight-month lead time to determine what the demand is going to be."

Global market dynamics, new indications and patient needs also make demand hard to predict. "As demand increases, manufacturers ramp up production, and at times, overshoot the estimated demand, which can result in a long market," explains Ground. "When this happens, manufacturers are forced to cool production until demand can catch up. And, when demand does catch back up with supply, a short market returns." To meet the different demands or to adjust capacity based on demand, manufacturers also can ship different parts of the protein product to different locations to ensure demand is met regardless of capacity constraints.

Currently, we're in a long market for IG, contributed to by the global demand for albumin, for which there is a shortage, especially from China, says Ground. When demand is high for one plasma protein therapy, enough plasma is available to increase capacity of other plasma protein therapies. In this

case, since there is an increased need for plasma donations to try to meet the demand for albumin, the other proteins such as IG that are collected from plasma donations must also be fractionated into protein therapies or else they go to waste. "But, if the relative demand for IG can't keep up with the relative demand for albumin in the ratio in which they are manufactured," says Ground, "there is an oversupply."

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The availability of plasma remains an uncertain limiting factor to increasing supply levels. To meet the demand for plasma protein therapies such as IG and albumin, manufacturers are continuing to expand their network of plasma collection centers. For instance, in just the past year, CSL Behring has opened 18 centers in the U.S. In October, the company and its subsidiary, CSL Plasma, saluted the contributions of plasma donors during International Plasma Awareness Week Oct. 12 through 18, at which they held a variety of activities in centers nationwide to promote greater understanding and appreciation among patients, employees and donors.<sup>14</sup> At the end of October, Grifols hosted a ribbon-cutting ceremony for its fifth Talecris Plasma Resources Center in El Paso, Texas. The \$1.8 million, 15,800-square-foot facility includes new technologies and can accommodate 1,800 donors per week.<sup>15</sup> Grifols now has a network of 150 plasma donation centers across the U.S. Baxter Healthcare's BioLife Plasma Services also continues to expand its plasma collection centers throughout the U.S. with 13 centers having just opened or are scheduled to open within the next year.<sup>16</sup>

As the number of plasma donors increases, and as research for new indications for IG continues, manufacturers are expanding their plasma fractionation production facilities. CSL Behring will spend \$450 million over the next few years to expand its production facilities in the U.S. and Australia, with

a \$240 million investment into its Kankakee, Ill., facility that produces albumin and immune globulin and a \$210 million investment into its Broadmeadows plant in Melbourne, Australia.<sup>17</sup> Grifols has also expanded its three manufacturing sites in Clayton, N.C., Los Angeles and Barcelona, Spain, the company's global headquarters. The expansions include a new, 185,000-square-foot fractionation facility in Clayton and a new facility in Los Angeles dedicated to the production of IG therapies. These new facilities have increased the company's capacity to fractionate plasma from 8 million liters per year to 12 million liters in 2015. Grifols also opened a new plasma testing lab in San Marcos, Texas, where every plasma donation undergoes rigorous scientific analysis prior to being approved for use in manufacturing.<sup>18</sup> And, according to a statement by Baxter Healthcare, the company is "in the process of building a new state-of-the-art fractionation and production facility in the U.S., with commercial production scheduled to begin in 2018. In addition, [the company has] established an agreement with Dutch company Sanguin to provide additional fractionation capacity to supplement Baxter's capacity."

Whether the market for IG is long or short, distributors become a management tool for allocating the drug in a responsible way, getting the product out to the most immediate need. "As a distributor, our goal is to work with the manufacturers and providers with an understanding of what the providers' immediate need is, especially during a very intense shortage," explains Ground. "In a long market, it becomes more interesting because the manufacturers are trying to get as much product out to market, and we become a buffering system between them and the end user. This also creates an environment in which the market has the opportunity to expand into new areas of therapeutic uses."

### The Future of Supply

While there is currently no shortage of IG, history has shown that recalls and withdrawals can cause sudden and unexpected shortages at any time. Add to these possibilities the growing global demand and the list of indications currently being studied, and it's not a matter of if there will be a shortage, but when. For instance, had Baxter's study on IG to treat Alzheimer's disease met its endpoints, the industry would likely be facing a crisis right now. To be complacent and unprepared for such possibilities is to put patients' lives in danger.

"The wonderful thing about IG is its unwavering path toward dozens of undiscovered areas of therapeutic promise for thousands of patients globally," says Ground. "This is precisely why we must make every effort to be vigilant surrounding the global supply-and-demand ratio of IG and to work to try to keep those factors in balance. Being out of

balance creates challenges either way. This, of course, is easier said than done, given the always present possibility of manufacturing issues. Yet, this is an inextricable fact of the plasma industry. We must strive to nurture demand, while delicately balancing this with managed increases in manufacturers' global capacity."<sup>6</sup> ❖

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