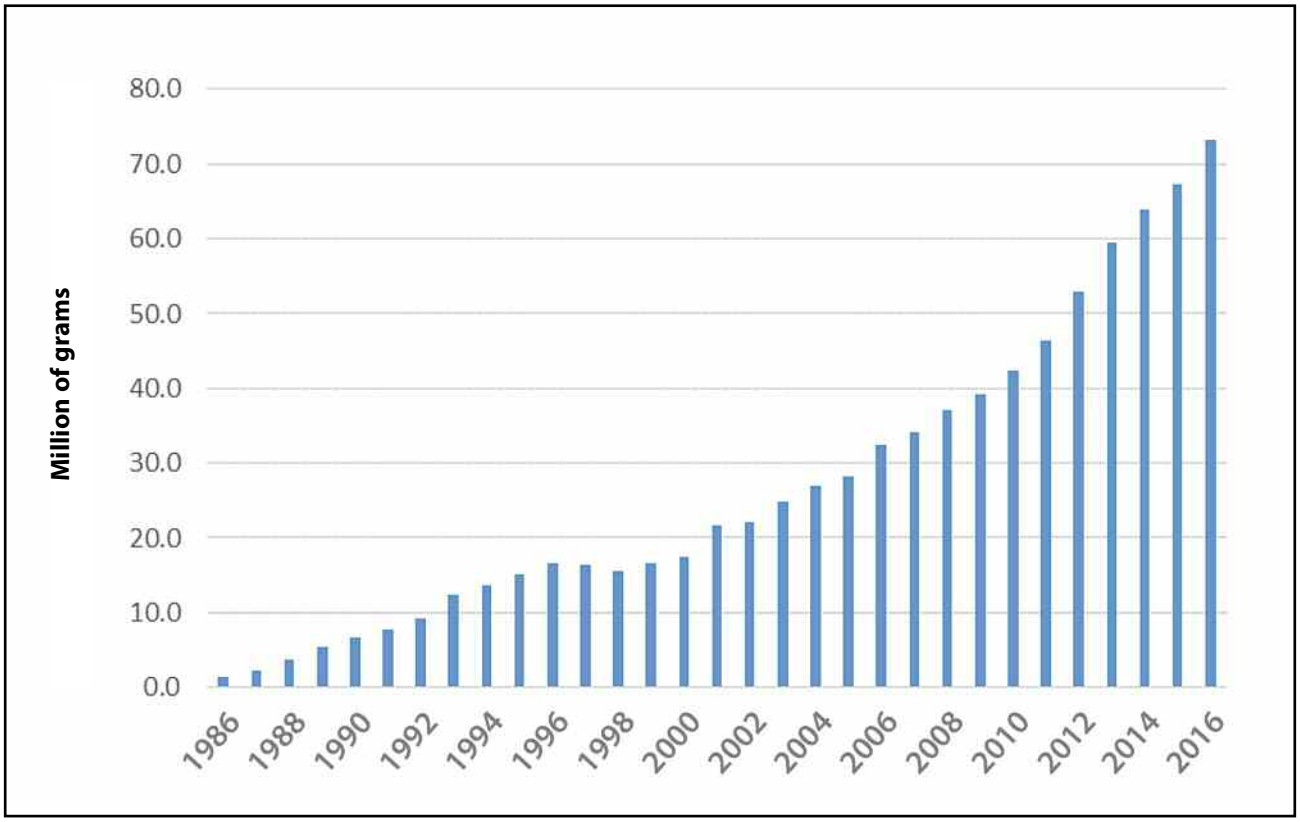
Plasma Fractionation: *The Challenge of Keeping Pace with Global IG Demand*

By Keith Berman, MPH, MBA

TRY TO NAME an injectable drug or biopharmaceutical available more than 30 years, whose prescribing activity has increased year after year without interruption — including a doubling in demand over the last decade. If you came up with polyvalent human immune globulin (IG) — which comprises intravenous immune globulin (IVIG) and essentially the same product formulated for subcutaneous delivery (SCIG) — you are correct.

If no others come to mind, it is because no other U.S. Food and Drug Administration (FDA)-approved drug entity has experienced anything resembling this sustained record of near-continuous demand growth* since FDA approved the first IVIG product in 1981 (Figure 1). Today, 15 IVIG and SCIG products (Table) compete for a share of a

Figure 1. The U.S. Polyvalent IG Market (IVIG/SCIG) from 1986 to 2016



Source: The Marketing Research Bureau, Inc. (Orange, CT)

** Excepting a product supply shortage period that extended from 1998 through 2001.*

U.S. hospital, clinic and home infusion market currently growing at more than 8 percent annually.

After a new drug is introduced, it typically goes through a market life cycle that culminates either with market *maturity* — demand stagnation once a product reaches its clinical applicability and market size limits — or with market *decline*, as providers switch to better new drug alternatives. Why has this not been the case with polyvalent IG? Industry experts have identified at least four reasons:

1) IG is essentially a concentrate of the most critical portion of the humoral immune systems of not one but thousands of individual plasma donors. Unlike single molecular entities, IVIG and SCIG products contain many thousands of highly specific IgG antibodies with a diversity of incompletely understood immunoregulatory, anti-inflammatory and infectious disease-targeting functions.

2) The clinical utility of IG across an ever-broadening spectrum of serious or life-threatening autoimmune, inflammatory, immunodeficiency and other immune-mediated disorders continues to be documented in patient studies and case reports now numbering in the thousands.

3) There is a trend toward more aggressive treatment with high-dose IG — 1 to 2 grams per kilogram of body weight or more per month — in autoimmune neurologic diseases in particular, based on evidence of superior effectiveness in relation to lower-dose regimens.[1,2] Additionally, long-term IG usage appears to account for a steadily increasing proportion of patients.[3]

4) While per capita utilization lags far behind North America and Europe, there has been a recent surge in IG demand in many countries in southeastern Asia. From 13 percent of global IG demand in 2008, just six years later, Asia accounted for 18 percent of the global IG market.[4]

Table. Available FDA-Approved IG Products*

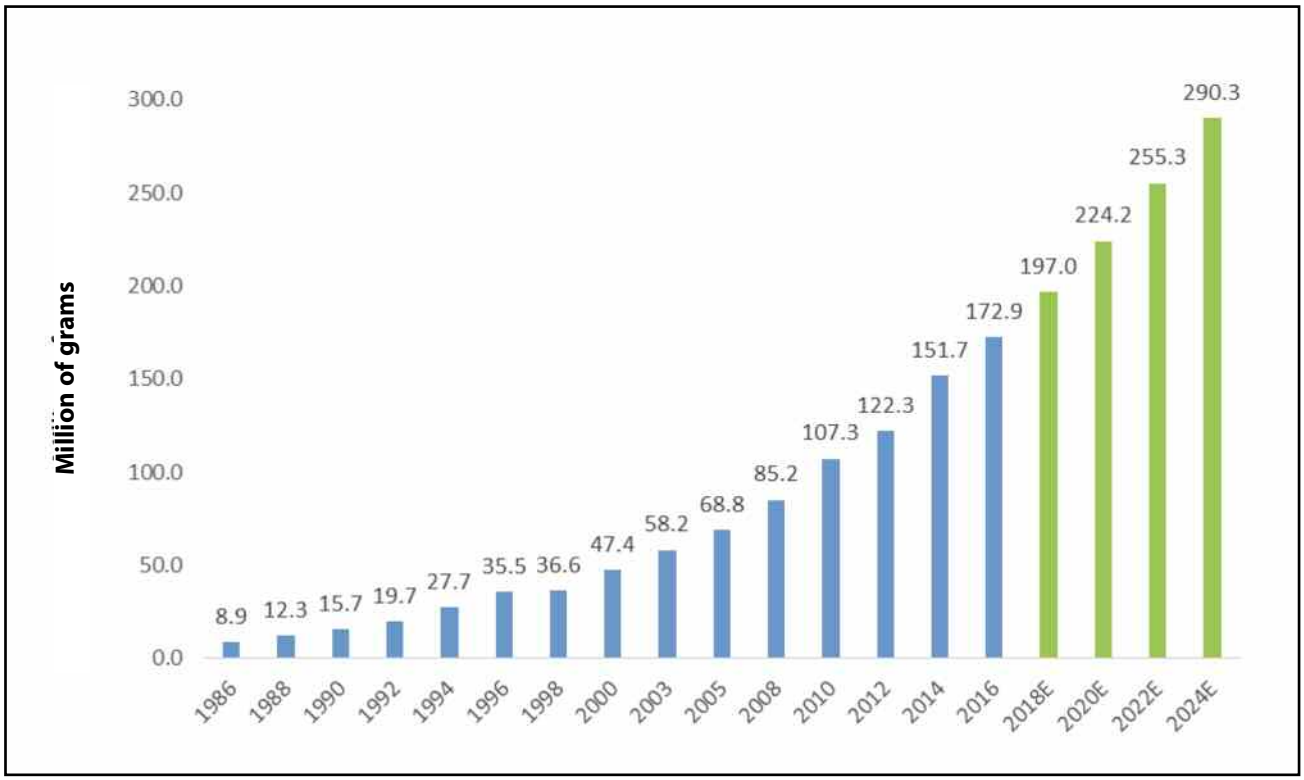
Manufacturer	*Product*	*Administration*
CSL Behring	Privigen Immune Globulin Intravenous (Human) 10%	Intravenous
	Carimune NF Immune Globulin Intravenous (Human) Nanofiltered**	
	HIZENTRA Immune Globulin Subcutaneous (Human) 20%	Subcutaneous
Grifols	Flebogamma 5% DIF Immune Globulin Intravenous (Human)	Intravenous
	Flebogamma 10% DIF Immune Globulin Intravenous (Human)	
	GAMUNEX-C Immune Globulin Injection (Human) 10%	Intravenous Subcutaneous
Shire	GAMMAGARD LIQUID Immune Globulin Infusion (Human) 10%	Intravenous Subcutaneous
	GAMMAGARD S/D Immune Globulin Intravenous (Human) 5%, less than 1 mcg of IgA per mL	Intravenous
	HyQvia Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase	Subcutaneous
	CUVITRU Immune Globulin Subcutaneous (Human) 20%	
Octapharma	Octagam Immune Globulin Intravenous (Human) 5%	Intravenous
	Octagam Immune Globulin Intravenous (Human) 10%	
Bio Products Laboratory (BPL)	Gammaplex Immune Globulin Intravenous (Human) 5%	Intravenous
	Gammaplex Immune Globulin Intravenous (Human) 10%	
Kedrion Biopharma	GAMMAKED Immune Globulin Injection (Human) 10%	Intravenous Subcutaneous

* All products are supplied in liquid form, except for Carimune NF and Gammagard S/D, which are supplied in lyophilized form.
** Production of Carimune NF is scheduled to be discontinued in Q3 2018.

In 2016, 35 years after IVIG was first introduced, U.S. demand for polyvalent IG products grew 8.7 percent, from 67.3 million grams to just over 73 million grams. Preliminary data indicate this trend continued through 2017, with product shipments exceeding 80 million grams. The global IG market mirrors this growth pattern: Over the eight years between 2008 and 2016, worldwide demand for IVIG and SCIG more than doubled, with an average annual growth rate of 9 percent (Figure 2).

IG demand growth on this scale presents two special challenges for the plasma fractionation industry. The first is to forecast and invest in plasma collection facilities to assure sufficient additional IgG-containing donor plasma is available to process into IG products. The second

Figure 2. The Global Polyvalent IG Market (IVIG/SCIG) from 1986 to 2016, with Projected Global Demand Through 2024



Source: The Marketing Research Bureau, Inc. (Orange, CT)

challenge is to plan, invest and provide adequate lead time to construct and secure regulatory approval to operate new or expanded fractionation and related IG production facilities.

It All Starts with the Plasma

Pooled donor plasma contains an average of around 9 grams of IgG per liter, but historically, most of that IgG was unrecoverable as a result of the process used to isolate it. The original Cohn plasma fractionation process, first developed in the 1940s to purify albumin, relied on sequential precipitation steps using increasing concentrations of cold ethanol, at the cost of a significant IgG yield loss.

As IVIG demand climbed in the 1990s, manufacturers began modifying their purification processes to try to improve the yield of IgG per liter of plasma. Today, most manufacturers employ just a single cold ethanol precipitation, substituting anion exchange chromatography and processing with agents such as caprylic acid to remove impurities.[5,6] "Over the last 25 years, plasma processing advances have improved IgG yield by roughly 60 percent on average, from 2.5 grams per liter to 4 grams or more per liter today," said plasma industry analyst Patrick Robert, PhD.[7]

While improved IgG yield per plasma liter has certainly helped moderate plasma requirements, manufacturers still must expand plasma collections at a pace to stay ahead of growing IG product demand. Consider the industry's four leading global manufacturers — Grifols, CSL Behring, Shire and Octapharma — which collectively supply nearly 70 percent of the world demand for IG products[4] and a similar share of the roughly 12 million additional IG grams purchased each successive year since 2012.

Assuming an IgG yield of 4 grams per liter, simple mathematics dictates that, in 2018, these four leading manufacturers will need to increase their combined plasma collections by approximately two million liters. As each individual plasma donation averages about two-thirds of a liter in volume, this translates into some three million additional plasma donations needed this year to keep up with growing global IG demand. That, in turn, translates into substantial investments in design and construction of new or expanded plasma collection centers, and additional equipment purchases and staffing.

Between 2004 and 2014, the global supply of plasma intended for fractionation

doubled to nearly 40 million liters (Figure 3). Looking forward, continuing investments in collection center construction, equipment and staffing will be needed to generate the additional three million or more liters of additional plasma required each year to meet the global IG demand forecast into the next decade.

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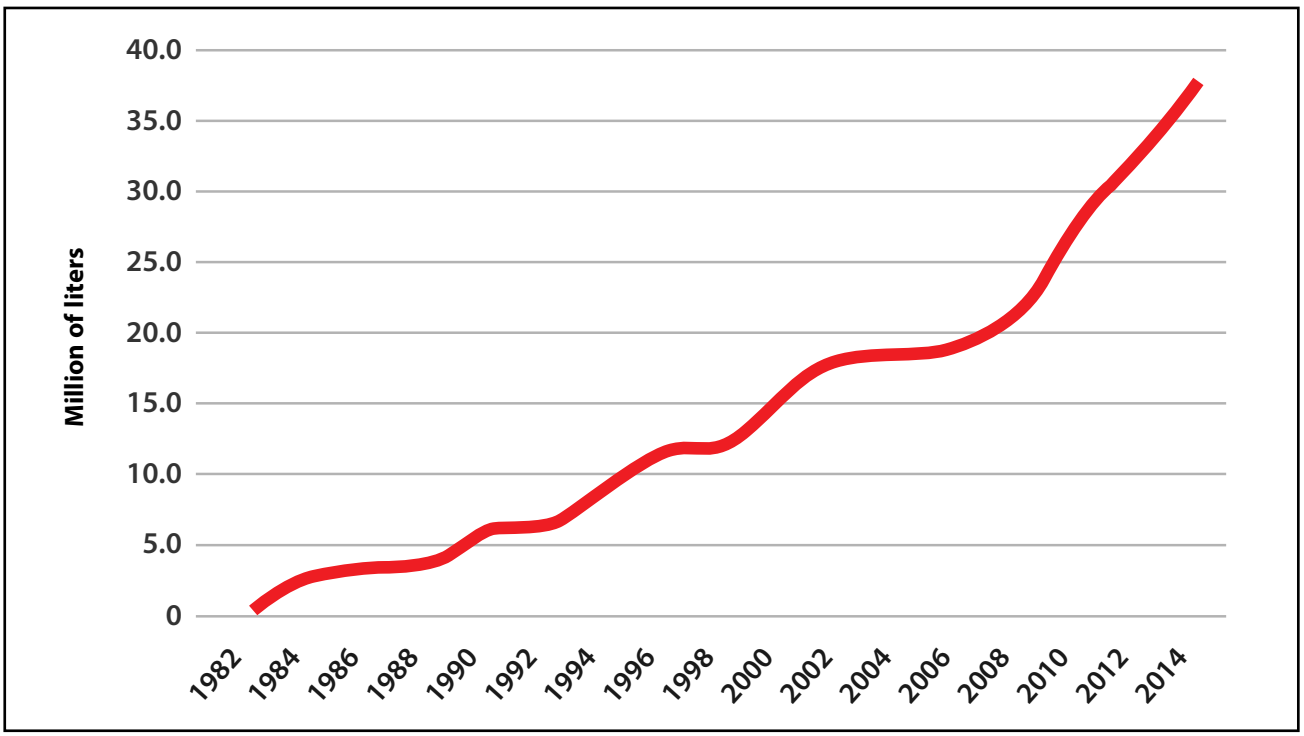
Major Investments in New Fractionation Capacity

At least two studies have compared the cost structure of plasma protein therapeutics and various chemical-based pharmaceuticals. For pharmaceuticals, manufacturing and raw material costs on average account for only about 15 percent to 20 percent of total costs, dwarfed by sales and marketing, research and development and other costs unrelated to production. The picture is entirely different for plasma protein therapeutics: Raw materials and manufacturing expense account for roughly 60 percent to 70 percent of total costs.[8,9]

Fractionating and purifying IgG from starting batches of thousands of liters of plasma requires custom-designed, scaled-up equipment housed in large physical plants operated by hundreds of specialized, highly skilled

Figure 3. Growth in Global Donor Plasma Requirements to Manufacture IVIG and SCIG



Source: The Marketing Research Bureau, Inc. (Orange, CT)

Left: CSL Behring Immune Globulin Production Facility at Bern, Switzerland[12]
Right: Grifols Plasma Fractionation Facility Under Construction at Clayton, North Carolina[13]

personnel (Figure 4). Often depending where existing production capabilities are located, a manufacturer may decide, in order to maximize operating efficiency, to situate all components of its IG manufacturing expansion — plasma fractionation, IgG purification, filling/finishing and final product testing — at a single facility or at multiple sites commonly spread across different continents. In scale, complexity and lead time, this investment dwarfs the typically $2 million to $3 million per-facility cost and two to three years to plan and open a plasma collection center.

Every major plasma fractionator is actively investing in new production capacity to keep ahead of forecasted future IG demand growth. One example of the scope and long planning time horizons involved is a nearly complete U.S.-based fractionation plant first announced in April 2012 by Baxter International,[10] prior to the spinoff of its plasma products division and eventual acquisition by Shire.

Baxter budgeted a capital investment in excess of $1 billion over a five-year period to build a facility with up to three million liters of annual plasma fractionation capacity when fully operational. In August 2012, ground was broken on the company's new state-of-the-art manufacturing facility in Covington, Ga., near Atlanta.[11] In December 2017, on schedule five years later, Shire filed for approval to manufacture its IVIG product, Gammagard Liquid, at the new facility. Commercial production is expected to start at the new Covington facility sometime in 2018.

A Commitment with a Higher Purpose

It's difficult to overstate the importance of the industry's commitment to proactively plan and invest in new plasma collection and IG production capacity. With the global IG market forecast to grow about 7 percent — nearly 15 million grams — annually through the year 2024, inadequate raw material or capacity, or both, could lead to a significant product shortage. A shortage would inevitably drive up prices and, more importantly, jeopardize the health of many thousands of thousands of patients who rely on IVIG and SCIG, both in the U.S. and across the globe.

In addition to the "big four" of Shire, Grifols, CSL Behring and Octapharma, a number of other experienced fractionators are stepping up their efforts to capture a piece of the growing IG market. South Korea-based Green Cross, for example, is completing construction of a plasma fractionation plant in Canada that will expand its 1.7 million-liter fractionation capacity by one million liters. Biotest in Germany is engaged in a project anticipated to double its current plasma processing capacity.

IG manufacturing is a costly, complex and globalized enterprise, but in the end, its success serves one higher purpose: assuring that today and in the future, patients in need have access to this unique therapeutic. ❖

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