Analysis of Supply, Distribution, Demand, and Access Issues Associated with Immune Globulin Intravenous (IGIV)

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ANALYSIS OF SUPPLY, DISTRIBUTION, DEMAND, AND ACCESS ISSUES ASSOCIATED WITH IMMUNE GLOBULIN INTRAVENOUS (IGIV)

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EXECUTIVE SUMMARY

Immune globulin intravenous (IGIV), also referred to as intravenous immune globulin (IVIG), is a valuable treatment for many seriously ill patients. Although the U.S. Food and Drug Administration (FDA) has not classified IGIV as being in shortage, some patients' groups and physicians have been reporting problems to the U.S. Department of Health and Human Services (DHHS) regarding access under current Medicare reimbursement levels. Some of the common complaints from patients and physicians include: increased difficulty in acquiring IGIV, switching from administration in a physician's office to a hospital outpatient facility, fewer treatments due to difficulty acquiring IGIV, and switching among IGIV products.

Performed under contract to the DHHS Assistant Secretary of Planning and Evaluation (ASPE), the primary objective of this study is an examination of IGIV market dynamics and the potential health consequences of IGIV access problems. To meet this objective, the study consists of the following three main components:

- An analysis of IGIV supply and distribution
- An analysis of IGIV demand and utilization, and
- An analysis of IGIV access problems, including their nature, size, and scope.

The main data sources for our analysis include: published studies from peer-reviewed journals and other trade publications; annual company and analyst reports of publicly traded IGIV manufacturers; research conducted and made available to us by patient groups, physicians, IGIV manufacturers, Centers for Medicare and Medicaid Services (CMS), National Blood Authority of Australia and the Department of Health and Human Services (DHHS) Advisory Committee on Blood Safety and Availability (ACBSA), and others; publicly and privately available databases, such as U.S. International Trade Commission Trade Statistics, IMS Health *National Sales Perspective*; discussions conducted with IGIV manufacturers, distributors (primary and secondary), group purchasing organizations (GPOs), hospital pharmacies (Federal and non-federal), specialty pharmacies, infusion centers, and physicians, and; comments received during the town hall meeting held on September 28, 2006, in Crystal City, Virginia to receive input from stakeholders.

E.1. IGIV SUPPLY AND DISTRIBUTION – KEY FINDINGS

→ In the United States, IGIV is supplied by five manufacturers: Talecris Biotherapeutics, ZLB Behring, Baxter BioScience, Grifols USA, and Octapharma USA. Together, these manufacturers currently market ten IGIV products in the U.S. Four of the products are in liquid form (Gammagard Liquid, Gamunex, Flebogamma, and Octagam) and the remaining six are in powder form (Carimune NF, Gammagard S/D, Gammar P-I.V., Iveegam EN, Polygam S/D, and Panglobulin).

→ In addition to intravenous products, there also is a newly licensed subcutaneous IGIV product, Vivaglobin, manufactured by ZLB Behring that entered the U.S. market in January 2006.

→ Discontinued or soon to be discontinued IGIV products, Gamimune N, Gammar-P I.V., Iveegam, Panglobulin, Sandoglobulin, and Venoglobulin (all lyophilized formulations), have been or are gradually disappearing from the marketplace. Further, new product introductions by existing manufacturers tend to replace older products and hence do not increase overall IGIV supply.

→ U.S. IGIV manufacturing is a tight oligopoly in which the leading three manufacturers, Talecris Biotherapeutics, ZLB Behring, and Baxter BioScience, have a combined market share of around 85 percent in terms of total IGIV grams sold.

→ There has been significant consolidation among plasma fractionators in recent years combined with plasma collection and fractionation capacity reductions. Even in light of these changes, however, IGIV available for distribution in the United States has steadily increased since 1998. In 1998, total IGIV available for distribution was 15.2 million grams, which has almost doubled to 28.3 million grams in 2005.

→ Recent increases in IGIV supply (from 2003 to 2005) are mainly attributable to the new market entrants, Octagam (Octapharma USA) and Flebogamma (Grifols USA), and substantial increases in Gamunex (Talecris Biotherapeutics) production. While some manufacturers are considering building new plants and enhancing existing facilities, getting these on-line will take a number of years. Thus, these considerations are not expected to have any short-run impacts on supply.

→ The possibility of new market entrants in the near future is uncertain as we cannot assess whether or when new IGIV products might be licensed for marketing in the United States. Moreover, even if new IGIV products may be available, the production capacities of most potential entrants are currently unknown.

→ Most IGIV manufacturers are currently operating near or at full capacity. Thus, U.S. IGIV availability is dependent upon the extent of IGIV sales to the rest of the world, adoption of high-yield fractionation technologies, and capacity enhancements. Plasma availability is also another bottleneck to increasing supply levels as indicated by IGIV manufacturers.

→ Over half of IGIV in the U.S. market is sold to non-federal hospitals. IGIV use by home healthcare and clinics, however, has been increasing significantly since 2001 and now accounts for more than 36 percent of IGIV sales combined.

→ Manufacturers are currently allocating IGIV to their customers. Under this allocation system, most customers are expected to justify their current IGIV use to the manufacturer to maintain and/or increase their allocations. In economic terms, current IGIV supplies are being rationed.

→ Home healthcare (i.e., home infusion companies, skilled nursing facilities, and specialty pharmacies) and clinics (i.e., outpatient clinics, surgical centers, family planning centers, group practice offices, and cancer treatment facilities) have a preference for liquid formulations, due to the convenience and the greater ease of administration. In contrast, non-federal hospitals tend to prefer the lyophilized IGIV products due to their lower cost.

→ Distribution of IGIV occurs through an authorized and a secondary channel. The IGIV marketplace has struggled with channel integrity and includes a significant secondary market outside of the authorized distribution channels. The secondary market is characterized by fluctuating prices and product availability. While the size of the secondary market is unknown, our analysis shows that it likely exceeds 10 percent of the total grams available for distribution.

→ The prevailing IGIV prices in the secondary market are substantially higher than those in the authorized channel.

→ The existence of a secondary market with high IGIV prices combined with a manufacturer instituted allocation system for IGIV are symptomatic of a market in which demand exceeds supply.

E.2. IGIV DEMAND – KEY FINDINGS

→ Demand for IGIV has risen sharply over the last decade. Although IGIV products are FDA-approved for only a handful of indications, IGIV is also used to treat numerous off-label indications. Medical evidence shows IGIV use to be beneficial and Medicare provides reimbursement for many off-label conditions, which represents 50 to 80 percent of total IGIV use. IGIV is also used for a variety of off-label uses where medical evidence is limited.

→ The largest share of IGIV is used for patients with neurological conditions, followed by primary immunodeficiency disorders.

→ GPOs have consistently stated that they would like to acquire more IGIV at current contract prices than is made available by manufacturers. The shortfall of supply relative to demand, looking forward to 2007, is roughly 14 percent, averaged over the GPO estimates. Even this shortfall is probably underestimated because existing demand is somewhat suppressed by hospital protocols and reimbursement problems.

→ In a survey of public hospitals, approximately 50 percent indicated that they cannot purchase enough IGIV to meet all patient needs. Further, 56 percent of the public hospitals reported that they had implemented a protocol to prioritize and monitor use of IGIV in their facilities. In a survey of 310 hospital pharmacy directors, the Immune Deficiency Foundation found that 27 percent of hospitals had instituted criteria for prioritizing IGIV use.

→ While manufacturers estimate annual IGIV demand growth between 6 to 8 percent, healthcare providers assert that demand is growing more rapidly at around 10 to 15 percent annually. This growth in demand is mainly driven by off-label uses.

→ Although there has been some decline in IGIV demand by physician's offices, IGIV demand by home infusion companies and hospitals is growing.

E.3. IGIV ACCESS PROBLEMS – KEY FINDINGS

→ Medicare reduced reimbursement rates for IGIV purchases with the introduction of the average sales price (ASP) methodology. Some healthcare providers are paying more than the average sales price plus 6 percent for IGIV and are not fully reimbursed.

→ Some healthcare providers have complained that they cannot purchase IGIV at the ASP plus 6 percent price or, in some cases, at close to this price. As of the second quarter of 2006, some healthcare providers are paying substantially more than ASP plus 6 percent to acquire IGIV based on data from IMS Health.

→ The Medicare payment rate in a quarter is based on the ASP from two-quarters prior. Thus, in a rising price environment, such as the 2005-2006 period, the ASP on which the Medicare payment rate is based will be lower than the actual ASP realized in the market during that quarter.

→ Except for homebound patients, Medicare is not designed to reimburse for more than the IGIV cost and does not cover the cost of infusion services (i.e., nursing time) in the home under Part B (which applies to home infusion therapy for patients with primary immunodeficiency) or Part D.

→ With the new reimbursement rules for physicians instituted in 2005, 42 percent of Medicare patients receiving IGIV therapy in physician's offices in the 4th quarter of 2004 had been shifted to other locations by the 1st quarter of 2006.

→ CMS data indicate that the total number of Medicare patients receiving IGIV at the hospital has increased between 2004 and the 1st quarter of 2006, as hospitals absorbed the patients previously receiving infusions at their physician's offices. Nevertheless, an Immune Deficiency Foundation (IDF) survey of hospital pharmacy directors showed that 32 percent of hospitals reported turning away patients for IGIV treatment at some point during 2006. No CMS data on the number of patients receiving IGIV in hospitals are available after the 1st quarter of 2006.

→ Home infusion services generally do not accept new primary immune deficiency (PI) patients with only Medicare coverage. These limitations in service are caused because healthcare providers (1) are not able to acquire IGIV at prices at or below the Medicare Part B reimbursement level, and (2) are not reimbursed for the infusion service.

→ Changes in Medicare reimbursement methodology, in addition to limited product availability, have caused some interruptions in and/or modifications of IGIV therapies. Otherwise, most hospitals reported that they have managed to obtain just enough IGIV to provide necessary therapies. To the extent hospital IGIV-use protocols are in place, hospitals can presumably prioritize IGIV effectively and avoid the most severe healthcare implications.

→ Forced brand-switching has been frequently cited as presenting difficulties for a number of patients. Overall, most patients can switch brands without difficulties and IGIV brands are becoming more substitutable over time. Nevertheless, some patients have been unable to accept the IGIV offered due to sensitivities to the product offered or complications with their medical conditions.

→ Patient transitions, such as from hospital care to home health care, can be difficult to arrange and patients frequently miss one or more infusions. The difficulties stem from the time needed for home health care companies to evaluate medical needs of the patient, to ascertain insurance coverage and to transfer medical information.

→ A survey by the Immune Deficiency Foundation (IDF) of access problems for primary immune deficiency patients indicate that 26 percent of Medicare patients and 10 percent of other patients experienced adverse health outcomes due to problems with IGIV access. The problems include greater frequency of hospitalization, infections, bronchitis, or other problems. Physician interviews also suggest more frequent problems obtaining IGIV therapy for Medicare-only patients.

→ We lack data on the experiences of neurology patients over the past two years. Because hospitals with the worst IGIV access problems might prioritize their uses and exclude many off-label uses, such as neurology uses, some of these patients might be excluded from IGIV therapy. While alternative therapies are generally available for neurology patients, some patients might not respond well to therapies other than IGIV.

→ Several physicians interviewed for the study described situations in which patient health was compromised when they were shifted from a physician's office to a hospital setting for IGIV infusions and/or when patients had difficulties and delays in receiving IGIV infusions. In selected interviews for this study, physicians judged that individual patient deaths had been influenced by lack of access to IGIV. The medical histories involved are extremely complex and the medical and reimbursement circumstances have not been independently verified. In an IDF survey of 152 immunologists, no physicians reported deaths due to IGIV access problems. Thus, the patient deaths identified appear to be fairly rare instances of severely negative health outcomes.

1. INTRODUCTION

Immune globulin intravenous (IGIV, also referred to as intravenous immune globulin (IVIG) is a plasma product that is used to treat patients with immune system disorders. IGIV has a number of on-label uses including treatment of humoral immunodeficiency, acute and chronic idiopathic thrombocytopenia purpura, B cell chronic lymphocytic leukemia (to prevent recurrent bacterial infections), Kawasaki disease, pediatric HIV, and bone marrow transplantation. IGIV is also used for off-label treatments including autoimmune, neurological, and systemic inflammatory conditions. According to the Department of Health and Human Services (DHHS) Advisory Committee on Blood Safety and Availability, more than half of IGIV use may be for off-label indications. Due at least in part to the increase in off-label uses, demand for IGIV has increased in recent years.

Manufacturers typically sell IGIV through group purchasing organizations (GPOs), through distributors, and directly to physicians and pharmacies. GPOs negotiate a price for their members, who can then purchase IGIV directly from the manufacturers at that price. IGIV is usually purchased by hospitals or physicians who typically administer the treatment in hospital outpatient centers and physician offices. Treatments are administered intravenously and typically require monitoring during infusion. There are also some IGIV products that target specific antigens, such as RhoGam or RSV-hyperimmune globulin, but these products with specific antibodies are not within the scope of this study.

In January 2005, Medicare shifted from average wholesale price (AWP) as the basis for reimbursement to average sales price (ASP) as required by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA). This shift reduced the reimbursement amount to physicians by 40 percent for the powder form of IGIV and by 15 percent for the liquid form of IGIV compared to the 2004 reimbursement rates. Although the ASP-based payment rates have been increasing over time narrowing these gaps, patient advocacy groups and physicians have been reporting difficulty acquiring IGIV. The FDA Center for Biologics Evaluation and Research (CBER), however, has not identified a shortage of IGIV. There have also been reports of IGIV being diverted to secondary markets with increases in prices.

1.1. STUDY OBJECTIVES

The primary objective of this study is to characterize the IGIV market and various access problems reported by patient groups and physicians. To serve that purpose, the study has three components:

- An analysis of the IGIV supply and distribution, including IGIV manufacturers, market shares, manufacturing practices, and pricing of IGIV products.
- An analysis of the demand for and utilization of IGIV products, including how they are prescribed, administered, and paid for.
- An analysis of any physician or patient problems with access to IGIV, including the nature, size, and scope of any problems.

The supply and distribution analysis examines how IGIV products (excluding immune globulins targeting specific antigens) are produced, the level of production, and how production relates to potential problems with supply and price. For example, factors such as lead time to produce IGIV, complexity of the production process, regulatory issues, collection of plasma, manufacturing processes and life cycle, storage shelf life, and supply of inputs all affect supply. The analysis also characterizes the supply chain

from the manufacturer to the patient by determining the various pathways from the manufacturer to the patient.

This supply analysis aims to answer the specific questions posed by the DHHS Assistant Secretary of Planning and Evaluation (ASPE) regarding IGIV supply and distribution. Specifically:

1. How is IGIV manufactured?
2. What are the distribution channels for IGIV?
3. Who are the major manufacturers of IGIV and what IGIV products do they manufacture?
4. What are the IGIV manufacturing capacities of these manufacturers?
5. What are the main trends in the supply of IGIV?
6. How is IGIV allocated among various distribution channels?
7. Is there a secondary market for IGIV and what is its effect on IGIV prices?
8. Are manufacturers able to meet current demand for IGIV?
9. How do IGIV prices vary across product lines, manufacturers, and distribution channels?
10. Is there a system for distributing IGIV for emergencies? What criteria do manufacturers use to fulfill emergency requests?

The demand analysis focuses on the current utilization of IGIV in various healthcare settings and for different indications. The specific questions the demand analysis aims to answer include the following:

1. How IGIV is administered in various healthcare settings?
2. What are the on- and off-label uses for IGIV?
3. What are the impacts of new uses on overall IGIV demand?
4. Are there differences among IGIV products?
5. Do physicians have preferences for certain IGIV products?

Finally, the analysis of access problems aims to address the following ASPE questions:

1. What difficulties do physicians, hospitals, and other healthcare providers have with access to IGIV, including different acquisition channels?
2. What difficulties do physicians, hospitals, and other healthcare providers have with reimbursement for IGIV?
3. Have any changes in prescribing or administration practices arisen from IGIV access or reimbursement difficulties?
4. What are the health consequences to patients of any changes in IGIV prescribing or administration?

1.2. DATA SOURCES

The study relies on a broad range of information sources. These include:

- Published studies from peer-reviewed journals and other trade publications.
- Annual company and analyst reports of publicly traded IGIV manufacturers.
- Research conducted and made available to us by patient groups, physicians, IGIV manufacturers, the Centers for Medicare and Medicaid Services (CMS), the National Blood Authority of Australia, the DHHS Advisory Committee on Blood Safety and Availability (ACBSA), and others.
- Publicly and privately available databases, such as U.S. International Trade Commission Trade Statistics, IMS Health *National Sales Perspective*, and CMS claims.
- Discussions with IGIV manufacturers, distributors (primary and secondary), group purchasing organizations (GPOs), hospital pharmacies (federal and non-federal), specialty pharmacies, infusion centers, and physicians.
- Input from stakeholders received during the town hall meeting held on September 28, 2006, in Crystal City, Virginia.

2. IGIV SUPPLY AND DISTRIBUTION

This section examines the supply and distribution system for IGIV. Section 2.1 presents the data sources used in this part of the analysis. Section 2.2 summarizes the relative strengths and weaknesses of our methodology. The IGIV manufacturing (i.e., fractionation) process is described in Section 2.3. That section also profiles IGIV manufacturers and the products they are licensed to market in the United States; further, it addresses the market supply and pricing of various IGIV products. Section 2.4 characterizes the distribution system for IGIV, including the authorized and secondary channels. The section concludes with a discussion of the role of GPOs, pharmacy benefit management companies (PBMs), and specialty pharmacies in the distribution of IGIV.

2.1. DATA SOURCES

Analysis in this chapter is based on IMS Health data, published studies from peer-reviewed journals and other trade publications, and discussions conducted with IGIV manufacturers, distributors (primary and secondary), GPOs, hospital pharmacies (federal and non-federal), specialty pharmacies, infusion centers, and physicians.

2.1.1. IMS Health Data

IMS Health's *National Sales Perspective* database estimates national sales of all pharmaceutical products (including injectables) to retail and non-retail channels. It is based on IMS Health's *Retail Perspective*™ and *Provider Perspective*™ audits.

The *Retail Perspective*™ (formerly U.S. Drugstore Audit) audit covers pharmaceutical products purchased by independent pharmacies, chain drugstores, proprietary stores, mail order, mass merchandisers, and food stores with pharmacies in the entire 50 United States. To collect the data for the *Retail Perspective*™ audit, IMS Health 1) microfilms drugstore purchase invoices and 2) collects warehouse withdrawal records on computer tape from wholesalers on a periodic basis.

The *Provider Perspective*™ audit is complementary to the *Retail Perspective*™ and covers sales of pharmaceutical products to non-federal hospitals, federal facilities, long-term care facilities, clinics, home healthcare, and health maintenance organizations (HMOs) in the United States. To collect the data for the *Provider Perspective*™ audit, IMS Health 1) microfilms purchase invoices (for direct purchases by non-federal hospitals only), 2) extracts data from computer tapes provided by manufacturers (for their direct sales to federal facilities, HMOs, clinics, and long-term care facilities), and 3) collects warehouse withdrawal records on computer tape from wholesalers on a periodic basis.

Combined, the two audits cover 100 percent of the market distribution channels for all pharmaceutical products in the United States and provide information on total units sold during a given period (month, quarter, and year basis), as well as the acquisition cost for those units. For this study, we acquired monthly sales data (units and dollars) for each of the IGIV brands sold in the United States during the January 1998 to June 2006 period. The data were disaggregated at the extended unit level, which allowed estimation of per-gram average acquisition cost per IGIV brand and channel.

2.1.2. Other Data

In addition to the IMS Health data, the analysis also uses published studies and reports for background information on the IGIV industry. These include studies from peer-reviewed journals and

industry trade publications, annual company and analyst reports of publicly traded IGIV manufacturers, research conducted by National Blood Authority of Australia and the ACBSA.

The ERG project team also conducted a series of informal but tailored interviews with IGIV manufacturers, distributors, GPOs, hospital and specialty pharmacies, infusion centers, home infusion companies, and physicians. As per 5 CFR §1320, these interviews were limited to nine entities for each type of organization and did not solicit the same information across different types of organizations. Table 2-1 provides a breakdown of the types of entities interviewed for the study.

Table 2-1: Breakdown of ERG Interviews with Stakeholders

Type of Entity	Number Interviewed	
	Number	Percent of Total
Group purchasing organization	7	15.2%
Home infusion company	5	10.9%
Hospital pharmacy	7	15.2%
Specialty pharmacy	2	4.3%
Infusion center	1	2.2%
Manufacturer	5	10.9%
Association and/or advocacy group	5	10.9%
Physician	6	13.0%
Private insurance provider	1	2.2%
Distributor (primary and/or secondary)	7	15.2%
Total	**46**	**100.0%**

These interviews were mostly qualitative in nature and sought further insight into the nature of IGIV manufacturing bottlenecks, how the IGIV drug distribution system works, important trends in the industry, potential sources of IGIV access problems, and the role of Medicare reimbursement rates in industry behavior. While we requested quantitative information from some of the entities interviewed, most did not have this type of information available and others declined to provide it due to confidentiality concerns. Thus, none of the quantitative and/or company-specific data presented in this section comes from these interviews.

The analysis also draws from over 120 comments received during the town hall meeting held on September 28, 2006, in Crystal City, Virginia, to receive input from stakeholders on supply, pricing, and access issues with IGIV.

2.2. STRENGTHS AND LIMITATIONS OF THE SUPPLY ANALYSIS

The analysis provided in this section is mainly descriptive and is based on a variety of sources. Overall, its key strength is its reliance on this wide array of sources to create a more comprehensive picture than would have been otherwise possible. Specifically:

- The supply analysis uses data from IMS Health's *National Sales Perspective*™, an important private sector database on pharmaceutical (including injectables) market prices. The database is widely used and accepted by industry, and has existed for a relatively long time. The data collection methodology does not involve self-reporting. Further, the reported prices reflect the true acquisition cost of IGIV products to the end-user (pharmacies, hospitals, home infusion companies, clinics, etc.) and thus account for the cost of distribution.

- We also undertook a comprehensive literature review and conducted informal discussions with a wide range of stakeholders to gain a more in-depth understanding of the IGIV market dynamics.

There are, however, a number of limitations to the data and our analysis. Specifically:

- While the *National Sales Perspective* database is widely used, IMS Health's exact methodology for sampling invoices and "scaling up" to form market estimates is not described. It is also well-known that IMS Health data do not properly capture the off-invoice discounts that purchasers may receive from manufacturers. Further, occasional problems may arise in computing prices by dividing revenues by standard units where there may be some errors in the determining the standard unit. The data are also subject to rounding problems and may not adequately capture sales in small quantities.

- Informal interviews are useful for gaining qualitative in-depth knowledge, but they lack the statistical rigor of a properly designed industry survey. Although our interviews with manufacturers, distributors, and GPOs are representative of the industry practices of those segments, we cannot assert the same for our interviews with hospital and specialty pharmacies and physicians.[1] Thus, the analysis fails to adequately characterize any regional and other end-user-specific issues related to IGIV access.

- The perspectives of the various entities interviewed naturally reflect the entities' self-interests. Although we tried to critically assess the accuracy and representativeness of the information obtained through these interviews, an objective evaluation was not always possible.

2.3. IGIV MANUFACTURING

2.3.1. Manufacturing Process

Immune globulin is a naturally occurring collection of highly specialized proteins known as antibodies. Antibodies, which can recognize foreign antigens and initiate the body's immune response against them, are created by healthy people in response to infectious agents and are found suspended in human plasma within the bloodstream. People with immune deficiency disorders lack the ability to create certain antibodies, and often require IGIV therapy to ensure at least a partial immune response against microorganisms.

IGIV manufacturing is complex and requires substantial upfront cash outlay and planning. The manufacturing process takes between seven and 12 months from plasma collection at donor centers to FDA lot release and involves the following main steps (ZLB Behring, 2006a; Birkofer, 2006):

- Plasma collection (plasmapheresis).

- Laboratory testing.

- Fractionation.

[1] We have interviewed all five manufacturers and the main IGIV distributors who distribute 80 to 90 percent of all IGIV in the United States. Our interviews also covered the key GPOs that contract with manufacturers and offer IGIV to their member organizations.

- Quality control (QC) testing and lot release.

IGIV manufacturing decisions depend not only on the market conditions for IGIV but also on the market conditions for other plasma-derived products and coagulation factors (e.g., Factor VIII, Factor IX, fibrinogen, and thrombin). Human plasma contains three major proteins – albumin, immunoglobulin G (IgG), and fibrinogen – and other proteins such as coagulation factors (i.e., Factor VIII and Factor IX), anticoagulant proteins (i.e., Protein C), and protease inhibitors (alpha-1 antitrypsin, antithrombin, and C1-inhibitor) (see Table 2-2). As outlined in Figure 2-1 in Section 2.3.1.3, manufacturers fractionate at least two or three products in addition to IGIV, such as albumin, Factor VIII, and Factor IX, from the same liter of plasma to maximize revenues (Burnoff, 2005-06). Although IGIV is currently one of the main drivers of production decisions, manufacturers aim to maintain balanced production of all of their plasma products and coagulation factors to maximize revenues per liter of plasma. Adverse market conditions in such markets as albumin can thus have significant impacts on IGIV supply.

Table 2-2: Composition of Human Plasma

Protein	Percent of Total
Albumin	64.25%
Immune globulin (IgG)	20.29%
Fibrinogen	5.07%
Alpha 2 Macro	4.40%
Alpha 1 AT	2.54%
Fibronectin	0.51%
Antithrombin	0.34%
Plasminogen	0.34%
C1-inhibitor	0.29%
Prothrombin	0.25%
Others [a]	1.69%
Von Willebrand Factor	0.02%
Factor XI	0.01%
Factor IX	0.01%
Protein C	0.01%
Factor VII	0.00%
Factor VIII	0.00%
Total	**100.00%**

Source: Burnoff, 2005-06
[a] Other therapeutically important proteins such as coagulation factors (e.g., Factors VIII and IX) and anticoagulants (e.g., Protein C) are present only in trace amounts.

2.3.1.1. Plasma Collection

IGIV is derived from human blood plasma collected during blood and plasma donations. The type of plasma obtained as a "byproduct" of whole blood collected during blood donations is typically referred to as "recovered plasma" and comes from unpaid volunteer donors. Plasma collected from plasma donations is commonly referred to as "source plasma" and comes from paid donors.[2] Due to increasing demand for plasma and plasma products, much of the world's plasma supply is now source plasma and is obtained through plasmapheresis. Plasmapheresis is the process for obtaining blood plasma without

[2] According to the Code of Federal Regulations and AABB Circular of Information, plasma is classified as source plasma, fresh frozen plasma, or recovered plasma based on collection method, time from collection to freezing, freezing temperature, storage expiration, shipping temperature, and allowable deviation (BPAC, 2005).

depleting the donor of other blood constituents by separating plasma from the whole blood and returning the rest to the donor's circulatory system. Because plasma protein regenerates relatively rapidly in the human body as compared to red blood cells, plasmapheresis allows for larger and more frequent collection of plasma from donors than a standard blood donation. Source plasma typically contains 20 to 30 percent more Factor VIII than does recovered plasma due to the logistical aspects of collection, dilution with anticoagulant, and rapid separation from cellular elements. In contrast, recovered plasma contains more IgG than source plasma. Portion of source plasma comes from the same set of donors and plasmapheresis, especially when intensively performed on the same donor, yields plasma containing less IgG (Burnoff, 2005-06). The composition of plasma used (source versus recovered) influences the industrial yield of the IGIV (i.e., number of grams of IGIV per liter of plasma), as well as Factor VIII fractionation process, thereby affecting production costs (Burnoff, 2005-06). Currently, recovered plasma constitutes around 30 percent of all plasma used in IGIV manufacturing. While some manufacturers use only source plasma, the share of recovered plasma can be as high as 50 percent of total plasma fractionated for others.

Although there is no established standard for minimum donor pool size, immune globulin preparations are typically derived from up to 60,000 individual donors to ensure antibody heterogeneity.[3] The 60,000-donor limit is a voluntary industry standard adopted in late 1990s in response to blood product safety concerns echoed in the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) report on donor pool size of immunoglobulin products (GAO, 1998; NIAID, 1998). Since individuals possess a range of different antibodies at various concentrations, heterogeneity increases the likelihood that the immune globulin preparation will include specific antibodies needed to target the largest possible range of viral and bacterial infections (Ballow, 2002). IgG is the most common type of antibody, making up about 80 percent of the body's total antibodies (HON, 2002). The fluid provided in IGIV therapy has at least 90 percent IgG (with small amounts of two other types of antibodies, IgA and IgM).

In the United States, all blood collection centers are either registered or licensed, and all plasma collection centers are licensed and regulated by the U.S. Food and Drug Administration (FDA). These facilities are subject to random FDA audits and inspection. They also must comply with FDA regulations for donor safety and product quality (PPTA, 2006). In Europe, the Council of Europe's Public Health Committee and its guidelines group on Blood Transfusion and Immunohaematology publish recommendations for the donation, storage and processing of blood and plasma products. However, these collection centers are regulated by the specific countries in which they are located (PPTA, 2006).

Cost of Plasma

Plasma is a very expensive raw material, representing between 40 to 60 percent of the costs of plasma products (Burnoff, 2005-06; Curling and Bryant, 2005; Bryant, 2004). Because manufacturers fractionate a number of plasma products from the same raw material, the cost allocation formulas among these products affect the pricing of IGIV, as well as other products. The formulas used vary among manufacturers based on product portfolio, driving products (i.e., albumin, IGIV, and Factor VIII) and market demand (Burnoff, 2005-06).

Table 2-3, adopted from Burnoff (2005-06), demonstrates the effect of one liter of plasma cost (valued at $110) on IGIV, albumin, Factor VIII, and Factor IX prices using an allocation of 40, 25, 25, and 10 percent, respectively, and average industry yields of these products as noted in Table 2-5. From

[3] The World Health Organization's original guidelines require more than 1,000 donors per lot (Martin, 2006).

the model depicted in the table, one can deduce that each $10 per liter increase in plasma price due to additional selection and testing criteria translates into $0.10, $1.14, $0.01, and $0.003 increase per unit in albumin, IGIV, Factor VIII, and Factor IX prices, respectively. If the $10 per liter in plasma price increase is solely allocated to IGIV, the respective IGIV price increase becomes $2.86 per gram. Evidently, the effect of plasma cost increases on product prices is indirectly correlated with the total number of products fractionated out of plasma and commercial yields.

Table 2-3: Sample Plasma Cost Allocation for Plasma Valued at $110 per Liter

Product	Yield Assumption (per Liter Plasma) [a]	Cost Sharing (%)	Cost Allocation ($)
Albumin	25 grams	25%	$1.10/gram
IgG	3.5 grams	40%	$1.14/gram
Factor VIII	185 iu	25%	$0.15/iu
Factor IX	300 iu	10%	$0.04/iu

Source: Burnoff, 2005-06
iu = International Units
[a] The yield assumptions represent the midpoint of the range provided in Table 2-5 for the various plasma products.

According to data from the Marketing Research Bureau (MRB), there has been an 8.3 percent increase in the real per-liter cost of source plasma over the 1998–2006 period, after correcting for inflation.[4] Similarly, the real cost of recovered plasma has also increased by around 12 percent during the same period. Most IGIV manufacturers note that plasma costs are expected to continue their upward trend in the future, putting increasing pressure on IGIV prices. The higher plasma costs are partially attributable to increasingly stringent FDA requirements for plasmapheresis centers, reductions in plasma supply through collection center closures and the shrinking population of eligible plasma donors, and increases in plasma exports due to increases in worldwide demand for plasma therapies and for U.S. plasma.

U.S. Plasma Exports

The U.S. International Trade Commission (ITC) is an independent Federal agency with broad investigative responsibilities on matters of trade. ITC also develops and maintains the on-line interactive tariff and trade dataweb, which provides access to current and historical U.S. trade data, compiled from the official statistics of the U.S. Department of Commerce, U.S. Census Bureau. ITC tracks all commodity shipments out of the U.S., including those that are inter-company transfers. According to the classification system used by ITC, exports of human blood plasma for fractionation purposes can be classified under the following four Harmonized Tariff Schedule (HTS) codes:

- HTS 3002100110 – Human Blood Plasma,
- HTS 3002100120 – Normal Human Blood Sera, Whether or not Freeze-dried ,
- HTS 3002100130 – Human Immune Blood Sera, and

[4] We used the average Consumer Price Index (CPI) to convert the nominal dollars reported by MRB to real dollars. CPI data, provided by the U.S. Bureau of Labor Statistics (BLS), represent changes in prices of all goods and services purchased for consumption by urban households (BLS, 2006). The CPI value for 2006 represents the latest monthly index value reported by BLS. The reported percentage increases correspond to 34.1 percent for source plasma and 38.1 percent for recovered plasma in nominal terms for the 1998–2006 period.

- HTS 3002100190 – Other Blood Fractions, not elsewhere classified.

For each of the above HTS codes, ITC reports the country of export, total quantity exported (in kilograms), and the value of exports (in dollars). To examine the trend for U.S. plasma exports, we tabulated the historical country-specific export statistics for each of these HTS codes from ITC's tariff and trade database. Next, we obtained the locations of (1) FDA-licensed fractionation plants from the CBER *Blood Establishment Registration and Product Listing* database, and (2) fractionation plants that are not FDA-licensed from MRB's *International Directory of Plasma Fractionators 2005*. We then mapped these plant locations onto the country-specific export data tabulated.

Because HTS 3002100120, HTS 3002100130, and HTS 3002100190 also include finished and intermediate plasma products, such as paste, in addition to human blood plasma, Table 2-4 presents the total exports of human blood plasma classified in HTS code 3002100110 only for the period January 1998 to August 2006, by destination.[5]

Table 2-4: Total U.S. Exports of Human Blood Plasma (HTS 3002100110) for January 1998–August 2006, by Destination

	Total Human Blood Plasma Exports (in Liters) [a] (HTS 3002100110)				
		Percent Going to Countries with . . . [b]			
Year	Amount (in Liters) [a]	FDA-Licensed Fractionation Plant	Fractionation Plant (Not FDA-licensed)	No Fractionation Plant	Total
1998	4,782,595	85.90%	13.95%	0.15%	100.00%
1999	4,351,240	78.41%	20.60%	0.99%	100.00%
2000	4,891,837	77.65%	18.12%	4.22%	100.00%
2001	6,187,981	78.53%	21.25%	0.22%	100.00%
2002	5,363,975	75.96%	23.74%	0.31%	100.00%
2003	5,065,634	85.09%	13.90%	1.01%	100.00%
2004	5,578,816	76.39%	22.00%	1.61%	100.00%
2005	6,161,961	66.71%	33.09%	0.19%	100.00%
2006 [c]	4,308,186	58.11%	41.52%	0.37%	100.00%

Source: ITC, 2006
[a] The U.S. ITC reports exports of human plasma in kilograms. We converted kilograms into liters for consistency using the specific gravity of human plasma at 4° C, which is 1.0310 (Trudnowski and Rico, 1974).
[b] The locations of FDA-licensed fractionation plants are obtained from the CBER Blood Establishment Registration and Product Listing database. The locations of fractionation plants that are not FDA-licensed are obtained from MRB's *International Directory of Plasma Fractionators 2005* (MRB, 2005). These locations are mapped onto country-specific export data provided by the U.S. ITC to generate the above tallies.
[c] Represents eight months of data.

As the table shows, U.S. exports of human blood plasma classified in HTS 3002100110 are increasingly going to countries in which there are fractionation plants that are not FDA-licensed (i.e., fractionation plants that supply plasma products to countries other than the United States). In 2005, over 33 percent of plasma exports in HTS 3002100110 were to countries where there are no FDA-licensed fractionation plants. In comparison, exports to these countries constituted only 14 percent of plasma exports in 1998. Total exports in the other three HTS codes have been relatively stable over the 1998-2006 period, with over 90 percent of all products classified in these codes going to countries where there are no FDA-licensed fractionation plants. The increase in plasma exports to countries with no FDA-

[5] The total export figures for HTS 3002100110 Human Blood Plasma underestimate actual plasma exports.

licensed fractionation plants combined with reductions in U.S. plasma collection capacity implies that there is less plasma available to fractionate IGIV for the U.S. market.[6]

2.3.1.2. Laboratory Testing

In the United States, each potential candidate for donation is subject to a medical exam, risk assessment, and viral testing. Initial plasma donations are tested for blood-borne pathogens, including human immunodeficiency virus (HIV) types 1 and 2 and hepatitis types B and C. Plasma donated by qualified subjects is often quarantined until the donor returns for a second round of assessments. Plasma collected from repeat, "qualified" donors is then pooled and re-tested. Only non-reactive plasma pools are released for further testing and IGIV manufacture. Any units that test positive for a virus are discarded (ZLB Behring, 2006a).

2.3.1.3. Fractionation

The next step in IGIV manufacturing involves fractionation of human plasma by the Cohn-Oncley method (see Figure 2-1) and derivations thereof, during which immune globulin along with other proteins are precipitated out of plasma by manipulation of solution pH, temperature, ionic strength, and ethanol content (Farrugia and Poulis, 2001).

Because of compositional differences between individual protein types, fractionation also allows for the separation of immune globulin component subclasses. These subclasses – IgG and IgA – possess different physical properties, and altering their concentrations within IGIV preparations can alter clinical results in patients (Martin, 2006). Additionally, the fractionation process can denature immune globulins, resulting in both altered protein structure and the creation of unwanted Ig polymers. Thus, for clinical preparations, the fractionation process seeks to obtain a high concentration of the desired Ig protein while minimizing undesirable modifications of antibodies to ensure patient tolerability and safety.

Emerging Fractionation Technologies

Increasing demand for IGIV has spurred the development of new fractionation processes, which allow for both improved specific Ig recovery (both in terms of quality and quantity) and the effective filtration and removal of viral and bacterial contamination (Martin, 2006). For example, Parkkinen et al. (2006) detail one new production procedure by which purified, polymer-free IgG is obtained through caprylic acid treatment, chromatography, nanofiltration, and ultrafiltration. This procedure increases the average yield of IgG grams per liter of plasma from 3.5 to 4 grams per liter in traditional preparations to 4.8 grams per liter. After purification, the final formulation of immune globulin is stabilized with sugars or gelatin, leaving a final product which typically contains more than 90 percent IgG.

Another promising technology is the Cascade process developed jointly by ProMetic Life Sciences, Ltd., and the American Red Cross. The Cascade process consists of a series of filtering steps specifically designed to extract the most valuable plasma proteins, such as IgG and Factor VIII. The process reportedly increases the commercial yields of plasma proteins by up to 80 percent and allows for the recovery of additional new proteins. The technology has the potential to be used by many plasma

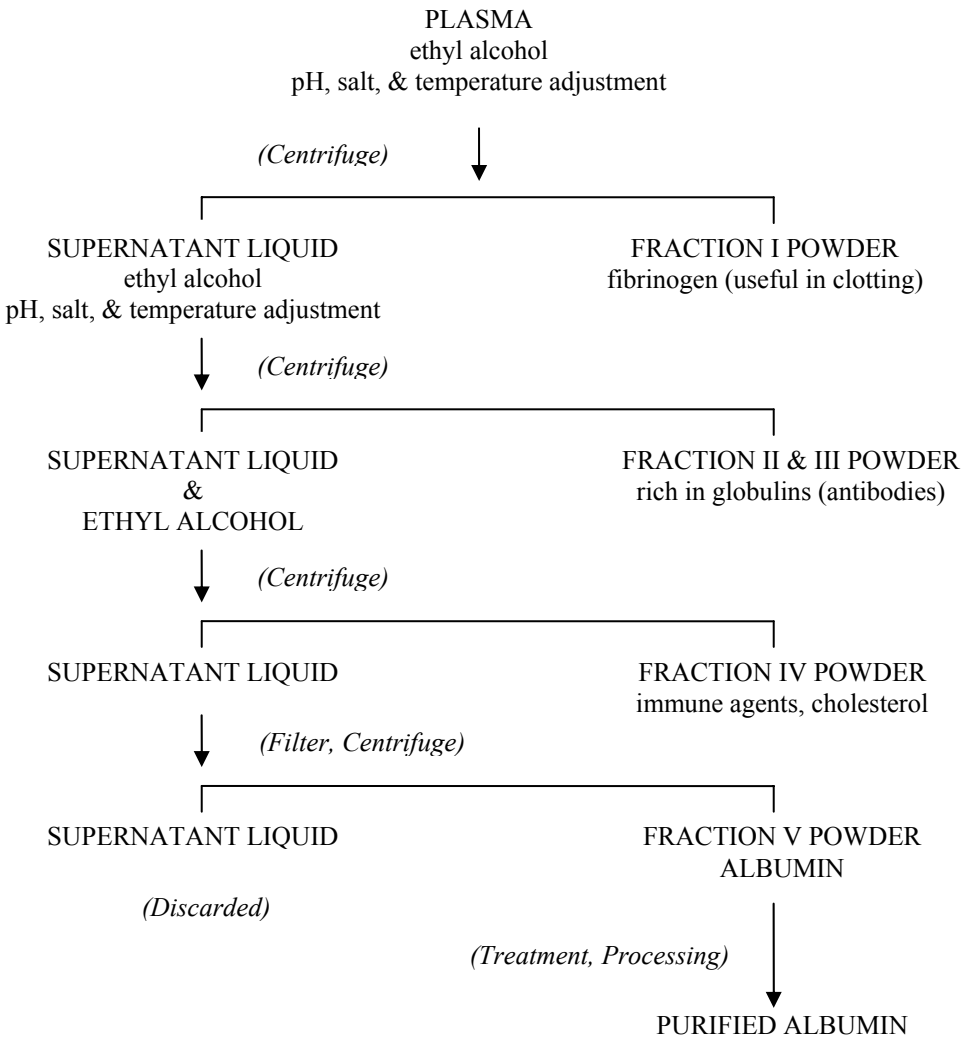
[6] As per FDA regulations, the plasma used in IGIV manufacturing needs to meet FDA regulatory standards and requirements (21 CFR Subchapter F). Although non-U.S. plasma can be fractionated into IGIV as long as the facility meets FDA requirements, IGIV manufacturers interviewed acquire the plasma for their IGIV products destined for the United States market from plasmapheresis centers located within the United States. This means that all IGIV marketed in the United States is in fact fractionated from U.S. plasma only.

fractionators. ProMetic Life Sciences, Ltd. has reported that it is in negotiations with a number of fractionators to license this technology (ProMetic, 2005).

Average Commercial Yields per Liter of Plasma

Table 2-5 presents the main plasma products fractionated, their use, and typical commercial yields per liter of plasma. As noted previously, most of the manufacturers fractionate at least three or four products from plasma although some, such as ZLB Behring, have larger product portfolios. The emerging fractionation technologies have the potential to substantially increase commercial yields for select proteins, such as IgG, Factor VIII, and Factor IX.

Figure 2-1: Cohn-Oncley Fractionation Process



Source: Starr, 2002

2.3.1.4. Quality Control (QC) Testing and Lot Release

Quality control testing occurs throughout the fractionation process and covers components, plasma pool, intermediates, bulk, and final product. The components, such as filters, vials, bottles, stoppers, and labels, are tested for purity and intended use. The manufacturer also tests the plasma pool and intermediates for purity, moisture and other characteristics. At the bulk stage, testing is performed to ensure potency, sterility, specific activity, and to check for pyrogens, osmalality, sodium content, and calcium content, as applicable. For final containers, the manufacturer performs many of the same tests that are conducted for the bulk product. The main focus of this QC testing, however, is the assurance of sterility. Some of the QC tests are one-day tests; others, especially those looking specifically at sterility, can take up to 14 days (Caplan, 1998).

Table 2-5: Main Plasma Products, Their Use, and Typical Commercial Yields per Liter of Plasma

Plasma Product	Typical Indication	Industrial Average Yield per Liter of Plasma [a]
Immune Globulins		
Immune globulin intramuscular	Infection prophylaxis	3–5 grams
Immune globulin intravenous	Antibody deficiency, infection prophylaxis, septicemia, transplantation, autoimmune disorders, such as ITP	3–4 grams
Special immune globulins	Anti-tetanus, anti-rubella, anti-pertussis, anti-cytomegalovirus, anti-tick-borne encephalitis, anti-hepatitis B, antivaricella, anti-respiratory syncytial virus	3–4 grams
Albumin	Emergency volume substitution, shock, burns	22–28 grams
Naturally occurring inhibitors (e.g., antithrombin)	To prevent certain types of pathological blood coagulation	NA
Coagulation Factors		
Factor VIII	Hemophilia A	120–250 iu
Factor IX	Hemophilia B	250–350 iu
Factor XIII	Factor XIII deficiency, wound healing	NA
von Willebrand Factor	von Willebrand disease	90–200 iu
Prothrombin complex concentrate (PCC, PPSB) Factors II, VII, IX, X	Acquired and hereditary deficiencies such as bleeding in newborns, inhibitors to factor VIII, hemophilia B	300–500 iu
Fibrin glue (fibrin sealant)	Numerous surgical uses to achieve sealing, hemostasis, or healing of tissues (topical applications)	NA

Source: WFH, 2004
NA = not available
iu = International Units
[a] Amounts indicate average yield per liter of plasma. Yields vary considerably according to manufacturing process.

Upon completion of QC testing, the test results and samples are submitted to CBER for lot release. CBER subsequently reviews the test results and protocol and determines whether it needs to conduct further testing prior to releasing the lot. The product may only be released into the distribution inventory upon receipt of the CBER release (Caplan, 1998). Companies with good regulatory history may obtain FDA exemption from lot release upon request.

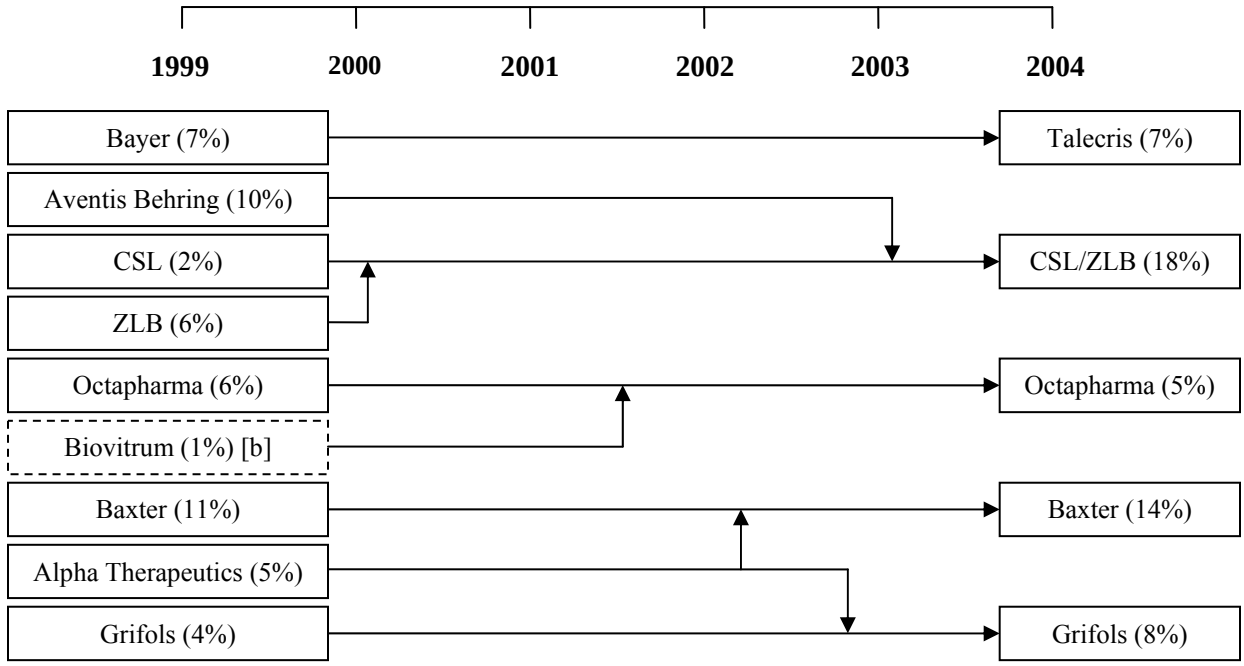
2.3.2. IGIV Manufacturers

The IGIV manufacturing industry has experienced major structural changes since 1990s due to FDA consent decrees, multiple dramatic drops in prices, significant increases in raw material (plasma),

and processing costs. The latter include inventory hold and plasma pool testing requirements (Curling and Bryant, 2005). Figure 2-2 presents the various mergers and acquisitions that took place as a result of these changes in the industry during the 1999 to 2004 period.

In addition to consolidation, there were significant reductions in the total amount of plasma fractionated during 2003 and 2004 in response to the dramatic drop in IGIV and albumin market prices. Between 2003 and 2004, Baxter BioScience closed 64 of its 161 plasma collection centers in the U.S. as well as its 700,000-liter capacity Michigan plant. These steps reduced their plasma collection and fractionation capacity from 4.6 million liters to 4 million liters.[7] In 2004, ZLB Behring closed down an additional 35 plasma collection centers, resulting in roughly a 10 percent decline (approximately 1 million liters) in overall plasma collection capacity (Haemonetics Corporation, 2004, 2006; Curling and Bryant, 2005).

Figure 2-2: Plasma Fractionators – Mergers and Acquisitions and Percentage Shares of World Fractionation Capacity, 1999–2004



Source: Farrugia and Robert, 2006; Turner, 2006
Note: The figures in parentheses represent the percentage share of world fractionation capacity.
[a] Formerly Centeon, L.L.C
[b] Biovitrum AB is a Swedish biopharmaceutical company and has sold its Plasma Products Division to Octapharma in July of 2002. Biovitrum AB has not had any U.S.-licensed IGIV products but has had agreement with Wyeth for the manufacture of a recombinant Factor VIII product (MPM Capital, 2002).

[7] Of the 64 plasma collection centers that were closed, 38 belonged to Alpha Therapeutics, which was acquired by Baxter BioScience in 2003. This has resulted in a 15 percent reduction in plasma collection capacity in the United States (Haemonetics Corporation, 2004, 2006).

2.3.2.1. IGIV Manufacturer Characteristics

At present, there are five manufacturers licensed to market IGIV in the United States: Baxter BioScience, Grifols USA, Octapharma USA, Talecris Biotherapeutics, and ZLB Behring. Of the five, only Baxter BioScience and Talecris Biotherapeutics are U.S.-based companies. Baxter BioScience operates fractionation plants in California and Austria, and Talecris Biotherapeutics operates a plant in North Carolina (CBER, 2006). Grifols USA, a Spanish-based company owned by Instituto Grifols S.A., runs plasma fractionation plants in Spain and California. These plants have manufacturing capacities of 2.1 million and 1.8 million liters of plasma, respectively (Probitas Pharma, 2003).

Octapharma USA is a subsidiary of Octapharma, a Swiss-based company with plasma fractionation plants in Austria, France, Sweden, and Mexico. The four fractionation plants have an overall manufacturing capacity of 2.2 million liters of plasma annually (Octapharma USA, 2006). Only those plants in Austria and Sweden, however, are FDA-licensed and supply IGIV to the U.S. market (CBER, 2006). Aethena Global (2006) estimates the capacity of Octapharma's Austrian plant at 1.1 million liters.

Finally, ZLB Behring is owned by an Australian holding company, CSL Ltd., and has FDA-licensed fractionation plants in Illinois, Switzerland, and Germany (CBER, 2006). According to the Probitas Pharma annual report (2003), ZLB Behring's total plasma fractionation capacity in 2003 was 6.2 million liters per year. This was reduced to approximately 5.2 million liters in 2004 with the closure of the company's Vienna, Austria, plant and the plasma throughput reductions at its Kankakee, Michigan, facility (Curling and Bryant, 2005; CSL Ltd., 2005).

According to data from the Marketing Research Bureau (MRB), the plant utilization ratios (i.e., the ratio of total plasma fractionated to capacity) of the five manufacturers that supply IGIV to the U.S. market range from 50 percent to 89 percent, with the majority of manufacturers having utilization ratios above 80 percent. Assuming full utilization of existing capacity and reported average yields for IGIV, Table 2-6 summarizes the total plasma fractionation capacity and potential IGIV output for these manufacturers.

Table 2-6: Worldwide FDA-Licensed Plasma Fractionation and IGIV Capacity, 2005

Company	Plasma Fractionation Capacity		Estimated IGIV Capacity	
	Liters per Year (1,000)	Percent of Total	Low Estimate (1,000 Grams) [a]	High Estimate (1,000 Grams) [b]
ZLB Behring	5,200	32.28%	15,600	20,800
Baxter BioScience	4,000	24.83%	12,000	16,000
Grifols USA	3,900	24.21%	11,700	15,600
Talecris Biotherapeutics	1,910	11.86%	5,730	7,640
Octapharma USA	1,100	6.83%	3,300	4,400
Worldwide total	16,110	100.00%	48,330	64,440

Source: Aethena Global Inc., 2006
[a] The low estimate is based on the assumption that a manufacturer can obtain 3 grams of IGIV from each liter of plasma on average.
[b] The low estimate is based on the assumption that a manufacturer can obtain 4 grams of IGIV from each liter of plasma on average.

The IGIV manufacturers interviewed for the study reported that they designate between 50 to as high as 85 percent of their total IGIV supply for distribution in the United States. After weighting the reported percentages by each company's IGIV sales share, we estimate that 60 to 70 percent of all IGIV fractionated by these companies is made available for distribution in the United States. This implies that the total grams of IGIV available for the U.S. can range from 31.4 (i.e., 48.3 million × 0.65) to 41.9 (i.e.,

64.4 million × 0.65) million grams under full utilization of capacity. Thus, an increase in IGIV supply to the U.S. market beyond this range requires less IGIV sales to other markets in the absence of capacity investments and implementation of improved yield technologies.

Table 2-7 presents the relative market share estimates for these IGIV manufacturers for the January 2003 to June 2006 period. From the table, the IGIV manufacturing industry is a tight oligopoly, in which the leading three manufacturers, Talecris Biotherapeutics, ZLB Behring, and Baxter BioScience, have a combined market share of around 85 percent, based on 2005 sales data from IMS Health.[8] The 2005 market shares of the remaining two manufacturers, Octapharma USA and Grifols USA, both of which entered the U.S. market in 2004, are around 9 and 6 percent, respectively.

Table 2-7: U.S. Market Share Estimates of IGIV Manufacturers, January 2003–June 2006 (% of Grams Sold)

Company	2003	2004	2005	2006	Average
Baxter BioScience	49.88%	34.96%	22.19%	22.41%	32.40%
Grifols USA	11.68%	3.04%	6.04%	7.89%	6.69%
Octapharma USA [a]	NA	0.20%	8.68%	5.58%	3.67%
Talecris Biotherapeutics [b]	1.08%	19.57%	31.99%	36.87%	21.91%
ZLB Behring	37.35%	42.22%	31.09%	27.25%	35.32%
Grand total	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**

Source: IMS Health, 2006
NA = not applicable
[a] Octapharma USA has entered the U.S. market in May 2004.
[b] Talecris Biotherapeutics acquired the contributed assets of the worldwide plasma business of Bayer Biological Products and became operational April 1, 2005.

The three large IGIV manufacturers, ZLB Behring, Baxter BioScience, and Talecris Biotherapeutics, are vertically integrated with their own plasma collection centers in the United States. According to the CBER *Blood Establishment Registration and Product Listing* database, ZLB Behring and Baxter BioScience currently own a total of 65 and 57 plasma collection facilities (in active status) in the United States, respectively.[9] Further, Talecris Biotherapeutics has recently announced that it has acquired a total of 58 plasmapheresis centers from International BioResources, LLC (Talecris, 2006a). Of the 58 centers, only 23 are currently active according to the CBER *Blood Establishment Registration and Product Listing* database. Among the smaller manufacturers, only Grifols USA self-sources plasma from the 57 plasmapheresis centers it owns under the BioMat USA Inc. name (CBER, 2006; Grifols USA, 2006). Octapharma USA purchases U.S. plasma from independently owned plasmapheresis centers and blood collection facilities in the United States.[10] Only one manufacturer interviewed for the study has tentative plans to increase the number of its plasma collection centers in the near future. Table 2-8

[8] By definition, a market is considered a tight oligopoly if three to four firms have a combined market share of over 60 percent (Shepherd, 1997).

[9] The ZLB Behring plasmapheresis centers are registered under the ZLB Bioplasma, Inc. name and Baxter BioScience plasma collection facilities are registered under the BioLife Plasma Services, L.P. name.

[10] As of December 2006, there are a total of 828 collection facilities, 332 plasmapheresis centers, and 195 community (non-hospital) and 767 hospital blood banks licensed in the United States that are in active status (CBER, 2006). Of the 332 plasmapheresis centers, 202 (61 percent) are owned by IGIV manufacturers.

summarizes the various characteristics of IGIV manufacturers that supply the U.S. market as discussed above.

Table 2-8: Summary of IGIV Manufacturer Characteristics

Company	Brand Name	2005 Market Share Estimate (% of Grams Sold)		Fractionation Plants (Fractionation Capacity in Million Liters)	Number of Plasma Collection Centers [g]
Baxter BioScience	Gammagard Liquid	0.09%	22.19%	California (2.7) Austria (1.3)	57
	Gammagard S/D	7.05%			
	Iveegam EN [a]	0.02%			
	Panglobulin [a]	2.49%			
	Polygam S/D [b]	12.53%			
Grifols USA	Flebogamma	6.04%	6.04%	California (1.8) Spain (2.1)	57
	Venoglobulin [c]	0.00%			
Octapharma USA	Octagam	8.68%	8.68%	Austria (1.1) [d] France Sweden (unknown) [d] Mexico	None
Talecris Biotherapeutics	Gamunex	31.99%	31.99%	North Carolina (1.91) New York [f]	23
ZLB Behring	Carimune	19.00%	31.09%	Illinois (2.0) [f] Switzerland (2.0) Germany (1.2)	65
	Gammar-P I.V. [a]	12.09%			
Total	NA	100.00%	100.00%	12 (16.11) [e]	202

Source: IMS Health, 2006; CBER, 2006; Octapharma, 2006; Aethena Global Inc., 2006; Talecris, 2006a
NA = not applicable
[a] Discontinued but still in some supplier inventories.
[b] Will be unavailable as of January 1, 2007.
[c] Venoglobulin was previously manufactured by Alpha Therapeutics and was purchased by Grifols Biologicals and then phased out.
[d] FDA-licensed facility.
[e] Only 10 of the 12 facilities are FDA-licensed and hence may supply IGIV to the U.S. market. The total plasma fractionation capacity reported excludes that of Octapharma USA's Sweden plant, whose capacity is unknown.
[f] Paste only.
[g] The number of plasma collection centers represents the number that is in active status based on CBER *Blood Establishment Registration and Product Listing* database. The figures may vary from those reported by others.

2.3.2.2. Potential Market Entrants

In addition to the five manufacturers, there are a number of other IGIV manufacturers that might be entering the U.S. market in the future. These include:

- Omrix Biopharmaceuticals – a biopharmaceutical company headquartered in New York, New York, with manufacturing facilities in Tel Aviv, Israel (Omrix Biopharmaceuticals, 2006).
- Lev Pharmaceuticals – a biopharmaceutical company focused on developing and commercializing therapeutic products for the treatment of inflammatory diseases that has recently entered into an exclusive license agreement relating to methods for producing plasma-derived IGIV (Lev Pharmaceuticals, 2006).

- Life Therapeutics – an Australian-based biotechnology company that uses new plasma separation technologies that allow high-yield production of therapeutic proteins (Life Therapeutics, 2006; Farrugia & Robert, 2006).

It is unclear whether and when any of these companies will actually enter the U.S. market, although the prospects for some of them are better than others. While the IGIV product development status of Lev Pharmaceuticals and Life Therapeutics is unknown, Omrix Biopharmaceuticals is currently conducting Phase III clinical trials in the U.S. for its IGIV product Omr-IgG-am for use in the treatment of primary immunodeficiency (PI). Moreover, FFF Enterprises, one of the largest distributors of IGIV in the United States, is sponsoring the active investigational drug application for Omr-IgG-am and will become the exclusive marketing agent and authorized distributor for the product for five years upon FDA approval (Omrix Biopharmaceuticals, 2006). Given its relatively small fractionation capacity at its Israel plant, however, it is unlikely that Omrix Biopharmaceuticals' entry into the U.S. market would have a significant effect on overall IGIV supply.

2.3.2.3. IGIV Products

The five IGIV manufacturers currently market 10 IGIV products in the United States: Carimune NF, Flebogamma 5%, Gammagard S/D, Gammagard Liquid, Gammar P-I.V, Gamunex, Iveegam EN, Panglobulin, Polygam S/D, and Octagam. Four of these products (Gammar P-I.V, Iveegam EN, Panglobulin, and Polygam S/D), however, have been discontinued or are being discontinued, and hence will not be available in 2007 (see Table 2-9). These companies also supply IGIV and other plasma-derived therapies to the rest of the world. In addition to the currently marketed IGIV products, there is a newly licensed IGIV product, Vivaglobin, manufactured by ZLB Behring. Vivaglobin has entered the U.S. market in January 2006. Unlike other IGIV products, Vivaglobin is for subcutaneous administration – below the surface of the skin and not into a vein – and can be self-administered (Vivaglobin, 2006).

Table 2-10 presents the relative market shares of various IGIV products as a percentage of total grams sold for the 2000 to June 2006 period. Older IGIV products (Gamimune N, Gammar-P I.V., Iveegam, Panglobulin, Sandoglobulin, and Venoglobulin) are gradually phased out with the introduction of new IGIV products. Gamunex by Talecris Biotherapeutics is the market leader as of 2005 (32 percent) followed by Carimune by ZLB Behring (19 percent), Polygam S/D by Baxter BioScience (12.5 percent) and Gammar-P I.V. also by ZLB Behring (12.1 percent).[11] Some manufacturers have new IGIV products in their pipeline and expect to begin marketing them upon FDA approval. As noted by one manufacturer, though, the new product launches are not expected to affect total IGIV availability in the U.S. market as they will be replacing older IGIV products.

Product Shelf-life

From Table 2-9, the liquid IGIV products can be effectively stored as a sterile 5 to 10 percent solution at 2º to 8º C (36º to 46º F) for 24 to 36 months with negligible degradation. When stored at elevated temperatures for prolonged periods of time (more than six months), however, physical decomposition occurs. Thus, these products require refrigeration during storage as well as transport. In contrast, lyophilized IGIV products can be stored at room temperature under 30º C (86º F) for 24 months. (Diemel et al., 2005).

[11] Baxter BioScience has announced that it will discontinue Polygam S/D as of January 1, 2007.

Table 2-9: IGIV Products Currently in Use in the United States

Company	Product	Method of Production	Form	Shelf-Life	Time to Infuse 35 grams	FDA-approved Indications
Baxter BioScience	Gammagard Liquid [a]	Cohn-Oncley fractionation; SD treatment; 35 nm nanofiltration; low Ph treatment	Liquid	24 months		PI
	Gammagard S/D	Cohn-Oncley fractionation; ultra-filtration; ion-exchange chromatography; solvent detergent treatment	Lyophilized	24 months	2.5 hours (5%) 0.6 hours (10%)	PI, ITP, CLL, KD
	Iveegam EN [b]	Cold ethanol fractionation; PEG; trypsin treatment	Lyophilized	24 months	5.6 hours	PI, KD
	Panglobulin [b]	Kistler Nitschmann fractionation; pH 4.0; trace pepsin; nanofiltration	Lyophilized	24 months	< 3.3 hours (6%)	PI, ITP
	Polygam S/D [c]	Cohn-Oncley fractionation; ultra-filtration; ion-exchange chromatography; solvent detergent treatment	Lyophilized	24 months	2.5 hours (5%) 0.6 hours (10%)	PI, ITP, CLL, KD
Grifols USA	Flebogamma	Cold alcohol fractionation; PEG ion-exchange chromatography; pasteurized at 60º C for 10 hours	Liquid	24 months	1.6 hours	PI
Octapharma USA	Octagam	Cohn-Oncley cold ethanol; fractionation; ultra-filtration; chromatography; solvent detergent treatment	Liquid	24 months	2.5 hours	PI
Talecris Biotherapeutics	Gamunex	Cohn-Oncley fractionation; caprylate/chromatography; purification; cloth and depth filtration; final container low pH incubation	Liquid	36 months	1.0 hour	PI, ITP
ZLB Behring	Carimune	Kistler Nitschmann fractionation; pH 4.0; trace pepsin; nanofiltration	Lyophilized	24 months	< 3.3 hours (6%)	PI, ITP
	Gammar-P I.V. [b]	Cohn-Oncley fractionation; ultra-filtration; pasteurization at 60° C for 10 hours	Lyophilized	24 months	2.8 hours	PI

Source: IDF, 2004; Thompson, 2005
[a] Information obtained from product insert. [b] Discontinued but still in some supplier inventories. [c] Will be unavailable as of January 1, 2007.
PI = primary immunodeficiency; ITP = immune thrombocytopenic purpura; BMT = bone marrow transplantation; HIV = pediatric HIV infection; CLL = B-cell chronic lymphocytic leukemia; KD = Kawasaki disease

Table 2-10: Market Shares of IGIV Products (as % of Grams Sold), 2000–June 2006

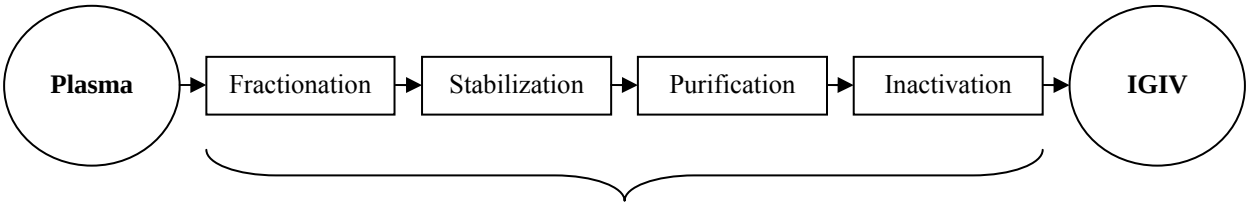
Brand Name	2000	2001	2002	2003	2004	2005	2006
Carimune	NA	8.59%	13.49%	16.14%	16.72%	19.00%	26.01%
Flebogamma [a]	NA	NA	NA	NA	1.18%	6.04%	7.89%
Gamimune N	26.13%	NA	NA	NA	NA	NA	NA
Gammagard Liquid [b]	NA	NA	NA	NA	NA	0.09%	3.01%
Gammagard S/D	17.03%	24.86%	22.19%	23.89%	9.26%	7.05%	3.72%
Gammar-P I.V.	10.33%	17.42%	19.49%	21.21%	25.50%	12.09%	1.24%
Gamunex [c]	NA	NA	NA	1.08%	19.57%	31.99%	36.87%
Iveegam	4.70%	2.35%	2.19%	0.72%	0.29%	0.02%	NA
Octagam [d]	NA	NA	NA	0.00%	0.20%	8.68%	5.58%
Panglobulin	7.67%	9.31%	12.39%	13.59%	5.05%	2.49%	1.48%
Polygam S/D	7.18%	28.02%	21.07%	11.68%	20.36%	12.53%	14.20%
Sandoglobulin	26.72%	6.92%	0.51%	NA	NA	NA	NA
Venoglobulin	0.24%	2.52%	8.66%	11.68%	1.87%	NA	NA
Total	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**	**100.00%**

Source: IMS Health, 2006; CBER, 2006
Note: Vivaglobin, a new ZLB Behring product, is not reported as it did not appear in IMS Health data provided.
NA = not applicable
[a] FDA licensed in December 2003.
[b] FDA licensed in February 2005.
[c] FDA licensed in August 2003.
[d] FDA licensed in May 2004.

Product Differences

As discussed in Section 2.3.1, manufacturers employ different production processes that can result in critical differences in the biologic activity of the IgG molecule. Figure 2-3 illustrates the critical steps between plasma procurement and the final IGIV product during which product differences are introduced. As many of the manufacturing steps may differ among the products, it is not surprising that the IGIV products currently marketed in the U.S. are not identical. Further, there is substantial variation in manufacturing, fractionation, and bottling process times that may also influence the biologic activity of the final product. IGIV products also differ in terms of their formulation (liquid vs. lyophilized), volume load, sodium content, sugar content, osmalality, IgA content, and pH (Gelfand, 2006).

Figure 2-3: Introduction of Product Differences in the IGIV Manufacturing Process



Source: Martin, 2006; Gelfand, 2006

IGIV product differences have the potential to affect clinical outcomes among patients with varying risk factors. For example, sodium content and/or osmolarity may be important considerations for both elderly and very young recipients, as well as those who may have cardiac disease or a risk for a thromboembolic event. Sugar content may be important for those who have diabetes or renal dysfunction (Gelfand, 2006; Siegel, 2006). Thus, the Clinical Immunology Society (CIS) recommends that a patient be matched with the appropriate IGIV product based on the characteristics presented in Table 2-11.

According to the medical literature, however, the pathogenesis and true incidence of adverse events associated with various IGIV products are unclear (also see Section 3). Published reports are mainly derived from anecdotal observations rather than properly designed trials. According to Durandy et al. (2005), the rates reported for the different products (e.g., data from package inserts) are difficult to compare because of the wide variability in how the actual incidence is generated and reported. Although the few controlled studies on the efficacy of various IGIV products have tended to support the concept that there is no "generic" IGIV, the medical literature does not currently offer conclusive evidence on how the product differences impact safety, tolerability, or efficacy (Gelfand, 2006; Durandy et al., 2005).

Table 2-11: Recommended IGIV Product Characteristics and Patient Risk Factors

Patient Risk Factor	Volume Load	Sugar	Sodium	Osmolarity	pH	IgA
Cardiac disease	●		●	●		
Renal disease	●	●	●	●		
Thrombosis risk	●		●	●		
Anti-IgA antibodies						●
Diabetic		●				
Elderly	●		●	●		
Neonate	●		●	●	●	

Source: CIS, 2006

Switching products can in some cases lead to adverse reactions ranging from mild (headache, nausea, fever, cough, etc.) to severe (renal failure, hyperviscosity syndrome, and aseptic meningitis). For example, data from the 2003 Immune Deficiency Foundation (IDF) survey indicates that 34 percent of all infusion-related adverse reactions occurred in the context of a product change (IDF, 2003). Thus, given the possibility of these adverse events, physicians prefer to keep a patient on the same IGIV product and are reluctant to start a patient on an IGIV product that is expected to be discontinued. Further, the American Academy of Allergy, Asthma and Immunology recommends "that anytime a product needs to be changed that the highest precautions be taken in administering the infusion due to heightened concern for adverse events" (AAAAI, 2006). That said, healthcare providers and pharmacists we interviewed have also indicated that they have been able to switch products without any serious adverse health consequences for the majority of their patients.

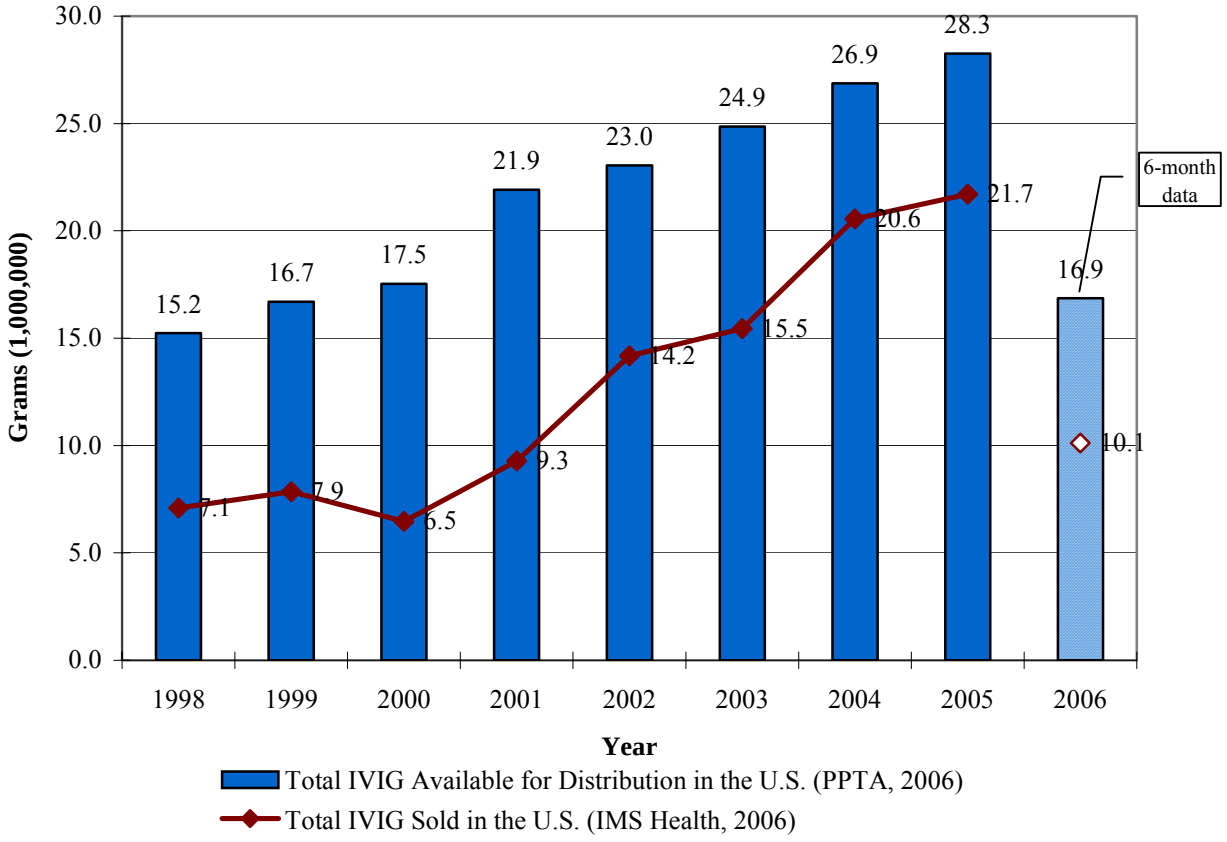
While manufacturers command a certain degree of "brand loyalty," there is some degree of substitutability among the various IGIV products. For example, hospital purchasers are sensitive to IGIV prices and have a preference for the lowest priced product. This price sensitivity of purchasers is also evidenced by distributors' observation that the lowest-priced IGIV product (Carimune NF) is the one that moves off warehouse shelves first, with the highest-priced product (Octagam) moving last.

2.3.4. Supply of IGIV

Despite the various plasma collection and fractionation capacity reductions discussed earlier, there have been increases in the total amount of IGIV made available for distribution in the United States over the 1998 to 2006 period, according to data reported by the Plasma Protein Therapeutics Association

(PPTA), a trade association representing IGIV manufacturers.[12] These figures, however, are larger than the total amount sold – i.e., pulled from a manufacturer or distributor warehouse by an end-user, such as a hospital, specialty pharmacy, home infusion company, etc. – for the same period as estimated from IMS Health (see Figure 2-4). As noted by one manufacturer, there is no guarantee that the total amount of IGIV reported as being available for distribution in the United States is in fact equivalent to the total amount actually sold in the United States for the given time period.

Figure 2-4: Total Amount of IGIV Available in the United States, January 1998–June 2006



Although its magnitude is surprising, the discrepancy between the PPTA reported figures and estimates derived from IMS Health may be due to:

- Data rounding and reporting problems associated with IMS *National Sales Perspective* data (see Section 2.2 for further discussion) – These may contribute the most to the discrepancy if a significant portion of IGIV is sold in relatively small quantities.
- Manufacturer and distributor product inventories.

[12] Each IGIV manufacturer reports the total amount being made available for distribution in the U.S. to Georgetown Economic Services, a third-party firm, on a monthly basis. Georgetown Economic Services in turn aggregates these data and reports the summary to PPTA. Each IGIV manufacturer also reports these figures to the U.S. FDA.

- Exports of IGIV to the rest of the world – Although manufacturers report the amount they made available for the U.S. market only, this does not rule out the possibility that some other market participants may be exporting some of the product on occasion as noted by one manufacturer.

Overall, the IMS Health data on sales underestimate the amount available for distribution by 20 to 60 percent over the January 1998 to June 2006 period. The magnitude of this discrepancy is smaller for later years. While most IGIV manufacturers assert that the PPTA-provided figures represent the amount of IGIV grams for the U.S. market only, we cannot confirm that the whole amount is actually sold, hence reached patients in the United States during the same period. We also cannot discern the relative contribution of each of the above factors to the discrepancy, if any.

2.3.4.1. A Closer Look at Supply

The PPTA figures on IGIV made available for distribution provide a partial picture of IGIV supply. A closer look at the sources for the increase (see Table 2-12) show that the supply increases have not been uniform across IGIV manufacturers or products. The overall increase in IGIV supply during the 2003 to 2005 period is mainly attributable to the new market entrants, Octagam (Octapharma) and Flebogamma (Grifols USA), as well as a substantial increase in Gamunex (Talecris Biotherapeutics) production. In fact, the total IGIV supply in 2005 would have been 10 percent lower than its 2004 level had Grifols USA and Octapharma USA been absent from the U.S. market.

Table 2-12: Change in IGIV Supply by Brand, 1998–2005

Brand Name	Period								
	1998	1999	2000	2001	2002	2003	2004	2005	Change from 2003–2005
Carimune	NA	NA	NA	1,883	3,109	4,013	4,494	5,368	1,355
Flebogamma [a]	NA	NA	NA	NA	NA	NA	317	1,707	1,707
Gamimune N	1,539	4,317	4,581	NA	NA	NA	NA	NA	NA
Gammagard Liquid	NA	NA	NA	NA	NA	NA	NA	26	26
Gammagard S/D	1,882	3,009	2,986	5,449	5,115	5,940	2,489	1,993	(3,947)
Gammar-P I.V.	1,936	483	1,811	3,818	4,493	5,274	6,855	3,417	(1,857)
Gamunex	NA	NA	NA	NA	NA	269	5,260	9,040	8,771
Iveegam	16	14	823	516	504	179	78	7	(172)
Octagam [a]	NA	NA	NA	NA	NA	NA	54	2,454	2,454
Panglobulin	387	1,200	1,345	2,041	2,856	3,379	1,357	703	(2,676)
Polygam S/D	2,435	1,541	1,258	6,142	4,857	2,904	5,473	3,541	637
Sandoglobulin	5,186	5,233	4,683	1,517	117	NA	NA	NA	NA
Venoglobulin	1,853	896	42	552	1,996	2,905	502	NA	(2,905)
Total [b]	15,234	16,693	17,530	21,916	23,046	24,861	26,879	28,257	**3,396**

Source: IMS Health, 2006
NA = not applicable
Note: The figures in parentheses denote negative values.
[a] Given the date of license for the product, the 2003–2005 change actually represents change from 2004 to 2005.
[b] The total grams sold reported by IMS Health are benchmarked to the total available for distribution figures reported by PPTA.

During the 2003 to 2005 period, there were also increases in the production of Carimune (ZLB Behring) and Polygam S/D (Baxter BioScience). There have also been substantial reductions in the production of other IGIV products, including Gammagard S/D, Iveegam EN, and Panglobulin by Baxter

BioScience; Gammar-P I.V. by ZLB Behring; and Venoglobulin by Grifols USA, over the 2003 to 2005 period. Several of these products are either discontinued or in the process of being discontinued.

Some IGIV manufacturers indicated that they are looking to expand their production capacity by building new fractionation plants and enhancing their existing facilities in the future. Others do not have any immediate plans for additional capacity. Even if additional capacity is built, getting these new facilities online will take a number of years. Thus, new production capacity by existing firms is not expected to have any short-run impacts on supply. While manufacturers indicated that they are able to meet their contractual obligations, they are unable to increase IGIV allocations of their existing customers or to accommodate new customers, based on our discussions with GPOs and distributors. Further, manufacturers expect to sell all of their 2006 IGIV production for the U.S. market, given their existing contracts. This implies a very tight supply situation in which a demand increase cannot be accommodated in the short run.

2.3.4.2. Meeting Emergency IGIV Requests

To meet emergency needs, each IGIV manufacturer has a toll-free telephone number that physicians can use to make an emergency IGIV request for their patients. General criteria for using these hotlines are that (PPTA, 2006):

- Requests must come from a physician.
- The clinical information needs to be evaluated.
- Physicians need to provide some form of documentation before product can be shipped.

One manufacturer stated that the physician must demonstrate that the patient's indication is one of the FDA-approved uses and that the patient has contacted all of the authorized distributors of the manufacturer. Another manufacturer interviewed noted that it is the medical director who handles the decision as to whether the requests can be fulfilled.

All manufacturers set aside an inventory of IGIV to meet emergency requests. Most manufacturers, however, have very few emergency requests for their product. One manufacturer reported a flurry of emergency requests when they set up their emergency hotline and then again when Medicare revised its reimbursement strategy in the beginning of 2006. The notable exception is the manufacturer who reported that they currently receive 2 to 3 calls a day for product. This manufacturer fulfills these requests and as a result, has significantly depleted their emergency supply. Currently, this manufacturer defers the handling of such emergency requests to its authorized distributors. Other manufacturers indicated only filling a small number of emergency requests recently. Further, some manufacturers will only ship one dose, whereas others continue to support the patient's ongoing needs if necessary. Overall, little product volume seems to be provided in this way to patients.

2.3.4.3. IGIV Sales by Channel

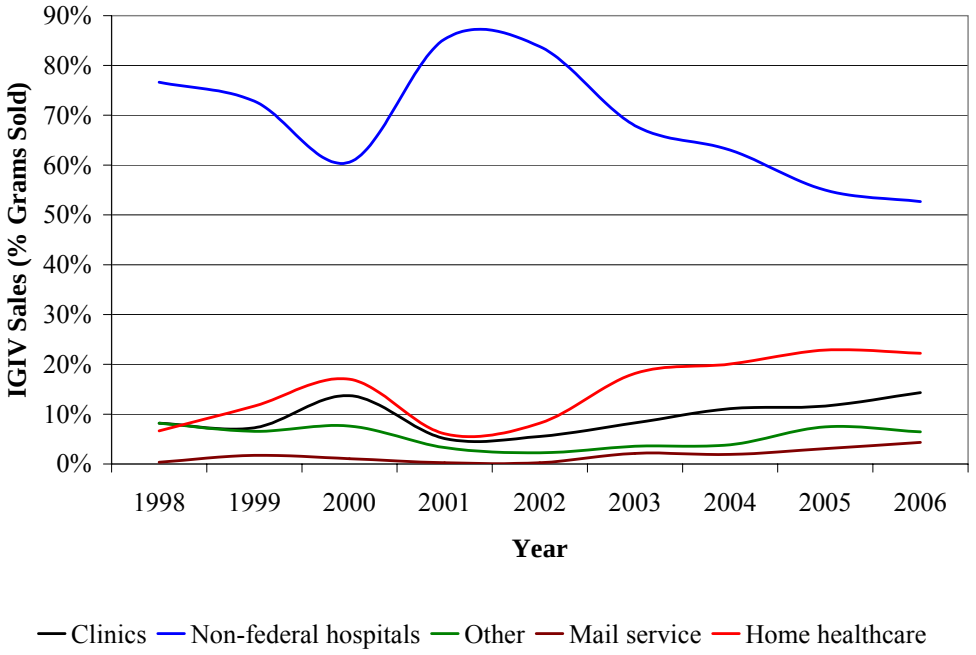
Figure 2-5 presents the distribution of IGIV among various retail and non-retail channels. [13] In 2005, non-federal hospitals were the largest users of IGIV (55 percent), followed by home healthcare (23

[13] Not every manufacturer interviewed for the study provided its sales breakdown by channel. Further, it is not possible to estimate the exact distribution of the product by sales channel based on data provided by manufacturers given that a portion of the product made available to authorized distributors is unencumbered and can be sold to any

percent), and clinics, which include physician's offices (12 percent). This distribution of IGIV use has remained practically unchanged in the first half of 2006 (January through June).

While non-federal hospitals have been the largest IGIV users historically, IGIV use by home healthcare and clinics has increased significantly from 2001 on. Our discussions with home healthcare companies and physicians also confirm this observed trend. It is interesting to note that during the 2001 to 2002 period, IGIV purchases by non-federal hospitals was significantly higher (around 85 percent) than in 2005, during which large numbers of Medicare patients were reportedly dislocated to hospitals from physician offices and home healthcare. One of the reasons for this could be the way "clinics" are defined in the IMS Health data. Clinics, as defined in the IMS Health data, not only includes physician's offices but also outpatient clinics (some of which may be affiliated with hospitals), surgical centers, family planning centers, and cancer treatment facilities. Further, the IGIV usage by Medicare beneficiaries only constitutes around 20 percent of total IGIV usage. Thus, even if some Medicare beneficiaries may be dislocated from physician's offices and home healthcare to hospitals, there may be increases in IGIV usage in physician's offices for their non-Medicare patients, offsetting this effect.

Figure 2-5: Sales of IGIV (% of Grams Sold), by Channel, January 1998–June 2006



Source: IMS Health, 2006
Note: The other category includes Federal facilities, chain stores, food stores, HMOs, long-term care facilities, and miscellaneous other establishments.

There does not appear to be significant variation in sales by IGIV product across the various sales channels (see Figure 2-6). The sales of Baxter BioScience products Gammagard Liquid and Gammagard S/D to non-federal hospitals have picked up in 2006 in response to the discontinuation of Iveegam EN, another product marketed by Baxter BioScience. Sales of Octagam to non-federal hospitals are lower than sales of other IGIV products, possibly because Octapharma USA does not have contracts with GPOs.

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channel, with some limitations (see Section 2.4 for further discussion). Thus, we think IMS Health data provide a more accurate estimate of IGIV sales by channel.

(Hospitals acquire most of their supplies through GPOs.) Home healthcare companies and clinics tend to have a preference for liquid formulations, possibly because they are easier to administer. In contrast, non-federal hospitals tend to prefer the lyophilized IGIV products due to their lower cost.

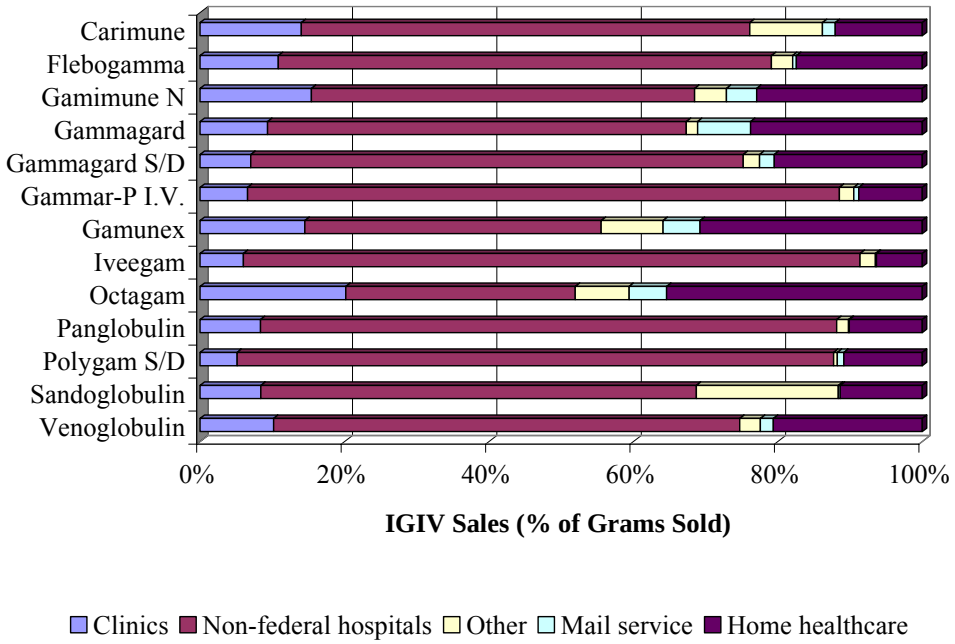
2.3.5. IGIV Pricing

IGIV sales prices are highly guarded and are determined by contracts between manufacturers and purchasers, such as GPOs, distributors, and healthcare providers. These contracts dictate pricing and/or quantities and are typically re-negotiated on an annual basis. For IGIV, which is on allocation, most contracts typically allow the price to adjust on a quarterly or more frequent basis. For example, one healthcare provider under GPO contract compared the IGIV pricing she receives from her supplier to the stock market, with prices fluctuating on a weekly basis.

The prices that various providers pay for IGIV vary depending on:

- The nature of their operations (hospital, physician's office, university research center, home infusion company, etc.).
- Whether they have contract protection (GPO contracts or direct contracts with manufacturers).
- The type of IGIV product (liquid vs. lyophilized) and brand (Carimune, Flebogamma, Gamunex, etc.) they use.

Figure 2-6: IGIV Product Sales, by Channel (% of Grams Sold), January 2005–June 2006



Source: IMS Health, 2006
Notes:
[a]The other category includes Federal facilities, chain stores, food stores, HMOs, long-term care facilities, and miscellaneous other establishments.
[b] The graph compares the percentage each value contributes to the total across all IGIV products.

2.3.5.1. ASP Methodology

As a result of the Medicare Prescription Drug Improvement and Modernization Act of 2003 (MMA), as of January 2005, Medicare began paying for IGIV (and other drugs classified under Part B) using an entirely new pricing methodology based on average sales prices (ASPs).[14] Prior to 2005, the pricing methodology for IGIV (and for most drugs under Part B) was based on the average wholesale price (AWP). For example, in 2004, the reimbursement amount for IGIV was based on 80 percent of the AWP as published in national pricing compendia, such as the "Red Book" (OIG DHHS, 2006). The Medicare allowance for IGIV is currently set at 106 percent of the ASP and separate ASPs are used to reimburse for liquid and lyophilized IGIV products.

2.3.5.2. IGIV Market Prices

We used IMS Health data to compute the volume-weighted average per-gram market prices for IGIV over time. The reported market prices in IMS Health approximate the actual prices that healthcare providers pay for IGIV, except for any off-invoice discounts. We also computed the volume weighted standard deviation for the average per-gram market prices as:

(1) $$\text{Weighted Standard Deviation} = \sqrt{\frac{1}{\left(\sum_i w_i\right) - 1} \times \sum_i w_i \left(x_i - \bar{x}_w\right)^2}$$

where i is month, w is the IGIV grams sold, x is the reported average per-gram price, and $\bar{x}_w$ is the volume-weighted average price.

Table 2-13 compares the average volume-weighted market prices for liquid and lyophilized products for 2005 through the second quarter of 2006 to Medicare Part B reimbursement rates for drug cost for the same period. From the table, the Medicare Part B reimbursement rates for liquid IGIV products are consistently over the average market prices. However, as can be observed from the weighted standard deviation figures, there is a $4 to $7 spread (i.e., standard deviation) in the actual market prices paid per gram of IGIV during the same period. In contrast, the reimbursement rates for lyophilized IGIV have been lower than the average market price for IGIV throughout the period, except for the first quarter of 2005. As for lyophilized IGIV, there is a much smaller spread around the average per-gram market price, ranging in magnitude from $6 to $7 per gram.

If we assume that the prices are normally distributed around the average, with some providers paying higher and others lower prices to acquire IGIV, then the percentage of market prices paid above the reimbursement rate can be estimated as:

(2) $$\%\text{ of Price Above Reimbursement} = P\left[Y > \left(ASP + 6\%\right)\right] = 1 - \int_{-\infty}^{ASP+6\%} \frac{1}{Std \times \sqrt{2\pi}} e^{\frac{-(y-Avg)^2}{2 \times Std^2}} dy$$

[14] The MMA defines an ASP as a manufacturer's sales of a drug to all purchasers in the United States in a calendar quarter divided by the total number of units of the drug sold by the manufacturer in that same quarter. The ASP is net of any price concessions such as volume discounts, prompt pay discounts, and cash discounts; free goods contingent on purchase requirements; charge-backs; and rebates other than those obtained through the Medicaid drug rebate program. Sales that are nominal in amount are exempted from the ASP calculation, as are sales excluded from the determination of "best price" in the Medicaid drug rebate program (OIG DHHS, 2006).

Table 2-13: Comparison of Medicare Part B Reimbursement Rates to IGIV Market Prices Across All Sales Channels, 2005 – Second Quarter 2006

		Liquid IGIV Price				Lyophilized IGIV Price			
Year	Qtr.	ASP+6%	Avg. [a]	Std. [b]	% > ASP+6% [c]	ASP+6%	Avg. [a]	Std. [b]	% > ASP+6% [c]
2005	1	$56.7	$52.5	$3.7	12.7%	$56.7	$42.5	$6.1	1.0%
	2	$56.2	$54.6	$6.3	39.6%	$39.5	$43.9	$6.5	75.0%
	3	$55.9	$54.7	$5.0	40.3%	$42.1	$44.3	$6.8	62.5%
	4	$56.3	$55.9	$6.6	47.4%	$43.1	$44.9	$6.8	60.3%
2006	1	$56.7	$58.6	$6.2	61.8%	$44.4	$49.3	$6.7	76.3%
	2	$58.2	$59.0	$6.6	55.1%	$44.5	$49.8	$6.0	80.7%

Source: CMS, 2006; IMS Health, 2006
[a] The average market price is a volume-weighted average of reported per gram acquisition prices.
[b] The standard deviation is weighted by grams sold and computed as noted in equation (1).
[c] The computation assumes that the prices paid for IGIV are normally distributed around their volume-weighted average value. The violation of the normality assumption necessarily affects computed percentages.

From Table 2-13, the percentage of market prices for liquid IGIV reported by IMS Health that exceed Medicare Part B reimbursement rates for drug cost range from 13 percent in the first quarter of 2005 to 55 percent in the same quarter of 2006. For lyophilized IGIV, the range for the percentage of prices that exceed Medicare Part B reimbursement rates for drug cost is 1 to 81 percent. It is important to note that these comparisons do not reveal any information on the *number* of providers that may be paying above reimbursement rates to acquire the product.

Pricing for Non-Federal Hospitals

Non-federal hospitals, which include private, city/county/state, and psychiatric hospitals, reportedly command better prices on both liquid and lyophilized IGIV products in comparison to other healthcare providers, given that a large majority has protection via GPO contracts. Table 2-14 reveals that the percentage of prices paid at or above the reimbursement rate by non-federal hospitals is higher for lyophilized IGIV (91.2 percent in the second quarter of 2006) than for liquid formulations (70.6 percent in the second quarter of 2006). One possible explanation for this is decreased supplies of lyophilized product in the market as manufacturers began shifting their productions to liquid formulations. A reduced supply combined with steady demand could have resulted in escalation of market prices for lyophilized products. This would explain why 78 and 91 percent of market prices paid in the first and second quarter of 2006, respectively, for lyophilized IGIV were above Medicare Part B reimbursement rates.

Pricing for Clinics

The pricing presented in Table 2-15 encompasses IGIV purchases by outpatient clinics, surgical centers, family planning centers, group practice offices, and cancer treatment facilities. As can be seen from Tables 2-14 and 2-15, clinics fare substantially worse than non-federal hospitals with respect to liquid IGIV, where 99.2 percent of market prices paid in the second quarter of 2006 were above Medicare Part B reimbursement rates. The pricing of lyophilized IGIV for these entities appears to have worsened in the second quarter of 2005 and then again in the first quarter of 2006.

Pricing for Home Healthcare

Table 2-16 presents the pricing for home healthcare facilities, which includes specialty pharmacies (i.e., closed door pharmacies) that service home healthcare. It is important to note that the

term "home healthcare" refers not only to Medicare-certified home healthcare providers but also to home infusion companies, skilled nursing facilities, and specialty pharmacies in the IMS Health data. As of the second quarter of 2006, the percentage of prices paid above Medicare Part B reimbursement rates by home healthcare companies is higher than those of non-federal hospitals but lower than those of clinics for liquid IGIV. The percentage of prices above Medicare Part B reimbursement rates for lyophilized products for home healthcare companies is comparable to those of non-federal hospitals, 92.5 percent in the second quarter of 2006. It is important to note that most of the large home healthcare companies also have access to GPO pricing similar to non-federal hospitals. In fact, some of the GPOs interviewed for the study indicated that around 40 percent of all IGIV they contract goes to alternate site healthcare providers, such as home healthcare facilities. Given the cost savings offered by home healthcare, private insurance payers have been increasingly pushing toward home-based IGIV infusions, which is reflected in the growth of that sector shown in Figure 2-5.

Table 2-14: Comparison of Medicare Part B Reimbursement Rates to IGIV Market Prices for Non-Federal Hospitals, 2005 – Second Quarter 2006

		Liquid IGIV Price				Lyophilized IGIV Price			
Year	Qtr.	ASP+6%	Avg. [a]	Std. [b]	% > ASP+6% [c]	ASP+6%	Avg. [a]	Std. [b]	%> ASP+6% [c]
2005	1	$56.7	$52.5	$2.6	NA	$56.7	$41.0	$2.5	NA
	2	$56.2	$54.9	$8.9	NA	$39.5	$42.4	$3.0	NA
	3	$55.9	$55.0	$2.4	NA	$42.1	$43.3	$2.3	NA
	4	$56.3	$56.1	$3.0	NA	$43.1	$44.3	$2.6	NA
2006	1	$56.7	$59.1	$2.1	87.4%	$44.4	$48.3	$5.1	77.8%
	2	$58.2	$59.3	$2.1	70.6%	$44.5	$49.9	$4.0	91.2%

Source: CMS, 2006; IMS Health, 2006
NA = not applicable
Note: The ASP + 6% reimbursement did not go into effect till January 1, 2006, for non-federal hospitals. Thus, the computations for 2005 are not presented.
[a] The average market price is a volume-weighted average of reported per gram acquisition prices.
[b] The standard deviation is weighted by grams sold and computed as noted in equation (1).
[c] The computation assumes that the prices paid for IGIV are normally distributed around their volume-weighted average value. The violation of the normality assumption necessarily affects computed percentages.

Table 2-15: Comparison of Medicare Part B Reimbursement Rates to IGIV Market Prices for Clinics, 2005 – Second Quarter 2006

		Liquid IGIV Price				Lyophilized IGIV Price			
Year	Qtr.	ASP+6%	Avg. [a]	Std. [b]	% > ASP+6% [c]	ASP+6%	Avg. [a]	Std. [b]	% > ASP+6% [c]
2005	1	$56.7	$53.2	$1.6	1.3%	$56.7	$45.3	$6.3	3.5%
	2	$56.2	$55.9	$6.4	48.1%	$39.5	$42.3	$5.1	71.0%
	3	$55.9	$56.6	$2.1	62.2%	$42.1	$44.0	$7.0	60.5%
	4	$56.3	$59.6	$2.4	91.8%	$43.1	$42.9	$7.7	48.8%
2006	1	$56.7	$62.1	$2.3	99.0%	$44.4	$50.9	$3.5	96.8%
	2	$58.2	$63.7	$2.3	99.2%	$44.5	$48.6	$5.5	77.0%

Source: CMS, 2006; IMS Health, 2006
[a] The average market price is a volume-weighted average of reported per gram acquisition prices.
[b] The standard deviation is weighted by grams sold and computed as noted in equation (1).
[c] The computation assumes that the prices paid for IGIV are normally distributed around their volume-weighted average value. The violation of the normality assumption necessarily affects computed percentages.

Table 2-16: Comparison of Medicare Part B Reimbursement Rates to IGIV Market Prices for Home Healthcare, 2005 – Second Quarter 2006

		Liquid IGIV Price				Lyophilized IGIV Price			
Year	Qtr.	ASP+6%	Avg. [a]	Std. [b]	% > ASP+6% [c]	ASP+6%	Avg. [a]	Std. [b]	% > ASP+6% [c]
2005	1	$56.7	$53.8	$2.0	7.0%	$56.7	$46.1	$4.9	1.5%
	2	$56.2	$55.9	$2.3	44.9%	$39.5	$46.8	$6.8	85.7%
	3	$55.9	$56.7	$1.7	67.5%	$42.1	$46.1	$3.2	89.4%
	4	$56.3	$58.4	$1.9	86.5%	$43.1	$48.1	$5.9	79.9%
2006	1	$56.7	$60.5	$2.5	93.7%	$44.4	$52.9	$6.0	91.8%
	2	$58.2	$61.2	$2.5	89.0%	$44.5	$52.2	$5.3	92.5%

Source: CMS, 2006; IMS Health, 2006
[a] The average market price is a volume-weighted average of reported per gram acquisition prices.
[b] The standard deviation is weighted by grams sold and computed as noted in equation (1).
[c] The computation assumes that the prices paid for IGIV are normally distributed around their volume-weighted average value. The violation of the normality assumption necessarily affects computed percentages.

Pricing for Mail Order Pharmacies

As can be observed from Figure 2-5, IGIV sales through mail order pharmacies have been increasing over time although overall sales through this channel constitute a very small share of total sales. Contrary to the other sales channels, mail order pharmacies tend to enjoy more favorable pricing for both lyophilized and liquid IGIV brands (see Table 2-17). For example, IMS Health data indicate that virtually all mail order pharmacies acquire IGIV at below Medicare Part B reimbursement rates since third quarter of 2005. Some of these mail order pharmacies may be associated with health insurance and/or pharmacy benefit management companies with direct contracts with IGIV manufacturers. This partially explains the typically lower prices paid by these entities to acquire IGIV.

Table 2-17: Comparison of Medicare Part B Reimbursement Rates to IGIV Market Prices for Mail Order Pharmacies, 2005 – Second Quarter 2006

		Liquid IGIV Price				Lyophilized IGIV Price			
Year	Qtr.	ASP+6%	Avg. [a]	Std. [b]	% > ASP+6% [c]	ASP+6%	Avg. [a]	Std. [b]	% > ASP+6% [c]
2005	1	$56.7	$43.3	$0.5	0.0%	$56.7	$37.4	$10.7	3.6%
	2	$56.2	$44.5	$11.3	15.0%	$39.5	$34.7	$13.1	35.7%
	3	$55.9	$44.1	$1.4	0.0%	$42.1	$33.9	$11.9	24.4%
	4	$56.3	$45.9	$1.8	0.0%	$43.1	$38.1	$9.3	29.4%
2006	1	$56.7	$48.5	$2.3	0.02%	$44.4	$34.3	$9.5	14.3%
	2	$58.2	$49.1	$3.5	0.4%	$44.5	$38.2	$8.3	22.3%

Source: CMS, 2006; IMS Health, 2006
[a] The average market price is a volume-weighted average of reported per gram acquisition prices.
[b] The standard deviation is weighted by grams sold and computed as noted in equation (1).
[c] The computation assumes that the prices paid for IGIV are normally distributed around their volume-weighted average value. The violation of the normality assumption necessarily affects computed percentages.

Pricing for 340B Entities

Section 340B of the Public Health Service Act ("PHS Act") and the related provisions of the Medicaid statute require IGIV manufacturers to agree to provide a discount to any healthcare provider that qualifies as a "covered entity" under that statutory provision or under §1927(a)(5) of the Social Security Act. These covered entities include various categories of "safety net" healthcare providers, such as nonprofit hospitals that have a high disproportionate share adjustment percentage, community health centers, AIDS clinics, and hemophilia treatment centers (PHPC, 2006).

There are no means of separating 340B entities in the IMS Health data to examine IGIV pricing for these entities. However, according to a recent survey conducted by the Public Hospital Pharmacy Coalition (PHPC), only 21 percent of their members (half of the covered entities in the U.S.) have been able to obtain any amount of IGIV at 340B discount prices. Additionally, even those hospitals able to access some 340B pricing on IGIV generally have had to purchase additional product at above-ceiling prices in order to adequately fulfill their patients' needs (PHPC, 2006).

2.3.5.3. IGIV Pricing Trends

As Figure 2-7 shows, average prices (volume-weighted and adjusted for inflation) for both liquid and lyophilized IGIV have dramatically dropped during the 2003 to 2004 period but have been steadily recovering since. For the first half of 2006, the average price for liquid and lyophilized IGIV is around $47.6 ($58.8 in nominal terms) and $40.1 ($49.5 in nominal terms) per gram, respectively. The upward trend in prices is expected to continue into 2007 based on information provided by IGIV manufacturers interviewed for the study.

2.4. IGIV DISTRIBUTION

Distribution of IGIV occurs through an authorized and a secondary channel. The authorized distribution channel is generally composed of manufacturer sales to authorized distributors and direct manufacturer sales to healthcare providers. Manufacturers require that authorized distributors sell directly to the healthcare provider. The secondary channel consists of distributors who mainly buy from other distributors rather than the manufacturer. Often the product changes hands several times before the patient receives it. Both lines of distribution are described in detail below.

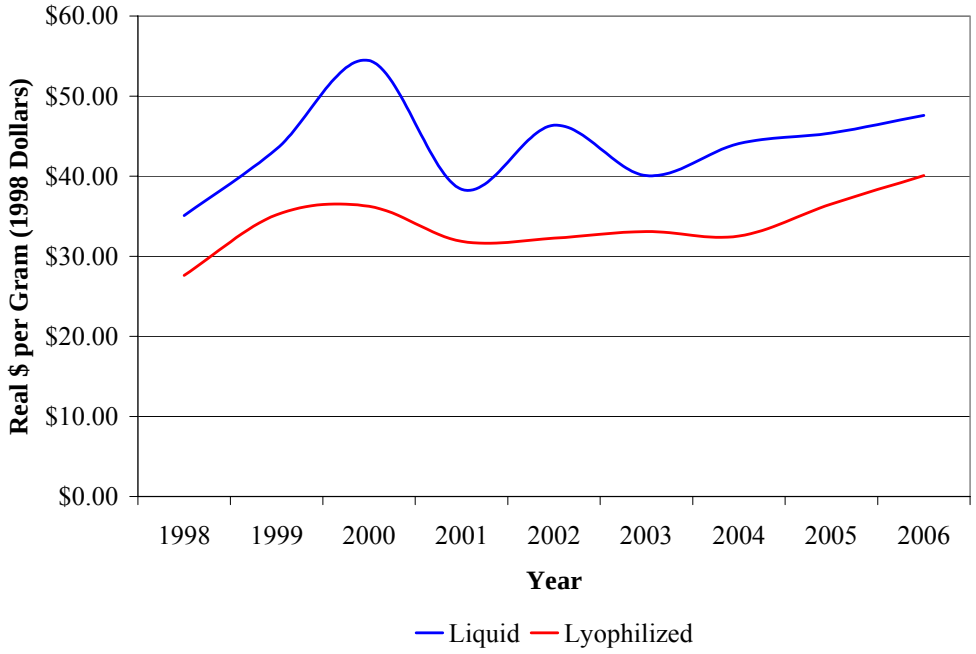
2.4.1. Authorized Distribution Channel

There are two broadly defined models of authorized IGIV distribution, although numerous additional variations could be defined in the secondary market.

2.4.1.1. Authorized Distributor Sales

The first model of drug distribution characterizes the movement of the majority of IGIV. Most IGIV products are shipped to authorized distributors and then sent to the provider, who administers the product. Each manufacturer has between two and nine authorized distributors (see Table 2-18). These entities distribute to home healthcare, including specialty pharmacies, hospital outpatient clinics, hospitals, physician offices, and infusion centers.

Figure 2-7: Average IGIV Market Prices (in 1998 Dollars), January 1998–June 2006



Source: IMS Health, 2006
Note: The average market price is a volume weighted average of monthly per gram acquisition prices. The computed nominal prices are adjusted by the Consumer Price Index (CPI). The CPI data are provided by the U.S. Bureau of Labor Statistics (BLS) and represent changes in prices of all goods and services purchased for consumption by urban households. The CPI value for 2006 represents the latest monthly index value reported by BLS. The computation is made using BLS inflation calculator provided at http://data.bls.gov/cgi-bin/cpicalc.pl.

Only two of the authorized distributors, ASD Healthcare and FFF Enterprises, are authorized to distribute all of the IGIV products currently marketed in the United States. The authorized distributor lists of two manufacturers, Baxter BioScience and Talecris Biotherapeutics, are publicly available on their company Web sites. Some manufacturers also use GPO-designated biological distributors, some of which might not appear on the list in Table 2-18. GPO-designated biological distributors have contracts with individual GPOs and manufacturers distribute to the GPO within the guidelines of these contracts.

In the last few years, in order to increase the integrity of the supply chain, each IGIV manufacturer has significantly reduced the number of its authorized distributors in the United States. Previously, manufacturers used large numbers of distributors, some of which were involved in reselling IGIV at a profit to other distributors (also known as the secondary market). By reducing the number of distributors to a small number of authorized distributors and restricting their sales to healthcare providers only in their contracts, manufacturers aim to reduce the amount of IGIV entering the secondary market. The secondary market, however, will continue to exist as long as 1) there are allocation contracts that limit free product flow from one healthcare channel to another (e.g., from physician's office to hospital) and 2) there is relatively inelastic patient demand for IGIV. The main concern with the secondary channel of distribution is the handling and high pricing of the product. Some manufacturers have approached providers in an attempt to trace product found in the secondary market to its source. The findings of these investigations are discussed further in the section on the secondary market. Most manufacturers interviewed reported having a policy to eliminate any business relationships with an entity that supplies the secondary market.

Table 2-18: Authorized Distributors of IGIV Products as of October 2006

Distributor	Number of IGIV Products Authorized to Distribute	Number of IGIV Products Distributed [a]
ASD Healthcare (subsidiary of AmeriSourceBergen)	10	10
Biocare	6	9
Blood Diagnostics, Inc.	4	8
Cardinal SPD	9	9
FFF Enterprises	10	10
Health Coalition	3	5
National Hospital Specialties	8	8
Prodigy Health Supplier Corporation	1	6
PSS World Medical, Inc.	1	1
Williams Medical Company	1	7

Source: Baxter BioScience, 2006; Talecris Biotherapeutics, 2006b; ERG interviews with IGIV manufacturers, 2006
[a] Some of these distributors may be GPO-designated ones and thus may distribute additional IGIV products that they are not considered "authorized" to distribute from a manufacturer's standpoint.

Based on our discussions with IGIV manufacturers, the majority of IGIV (80 to 90 percent) is distributed via authorized distributors on an allocation basis. Thus, the product is reserved for GPOs or healthcare providers, but warehoused by authorized or GPO-designated distributors. Some manufacturers also allow authorized distributors to sell product on the open market. Manufacturers and distributors noted that this product is intended only for sale to providers and usually constitutes a small percentage of total IGIV distribution inventory.

2.4.1.2. Direct Sales

Manufacturers also sell a portion of their supply directly to healthcare providers, such as university hospitals, physician's offices, and closed-door specialty pharmacies that typically service home healthcare. These sales are also typically on an allocation basis, involving an agreement between the manufacturer and the provider that governs both volume and price. Other non-allocation-basis sales are also governed by a price agreement between the manufacturer and provider but do not guarantee any volume. The latter type of price agreement constitutes a large portion of some manufacturers' business model (up to 30 to 50 percent).

2.4.2. Secondary Distribution Channel

The secondary distribution channel is composed of secondary wholesalers that generally do not offer a full line of pharmaceutical products, instead specializing in purchasing and selling pharmaceuticals that are often in short supply. For this analysis, this channel is defined as that in which any entity other than the manufacturer or authorized distributor sells IGIV to a healthcare provider. Secondary distributors do little advertising or sales promotion work other than periodic publishing of their sale prices, often via email or fax. Some of the products in the secondary distribution channel can change hands many times, moving from secondary distributor to secondary distributor. Thus, multiple transactions involving the resale of the product are commonplace. Cross-trading among distributors can also take place between authorized and secondary distributors (Siegel, 2005).

2.4.2.1. Sources of Product in the Secondary Channel

The level of activity in the secondary IGIV market varies, depending on the supply of IGIV available in the market. Pharmacies, physicians, and other healthcare providers note that there is

considerable variation in the volume of telephone calls, emails, and faxes from secondary distributors from month to month. Some have noted that the activity has decreased in recent months (i.e., in late 2006) and others have seen it pick up. A distributor noted that the activity itself probably has not changed, but that secondary distributors are more careful about documentation given recent criminal investigations into the secondary market activities of some wholesalers. Product in the secondary market generally originates from three different sources:

- Manufacturers selling product to secondary distributors.
- Authorized distributors selling product to secondary distributors.
- Healthcare providers and pharmacies reselling unused product.

Manufacturers Selling Product to Secondary Distributors

While IGIV manufacturers contend that they only sell to authorized distributors and providers, input from other sources contradicts this assertion. One GPO interviewed for the study reported that some manufacturers do indeed sell to secondary distributors at prices higher than that for allocated IGIV. Further, a secondary distributor interviewed for the study also indicated buying IGIV they sell directly from an IGIV manufacturer. In some cases, manufacturers and secondary distributors might have long relationships that manufacturers find difficult or unprofitable to sever. Due to manufacturers' desire for greater control of their product sales, however, this is judged not to be a large source of product in the secondary channel.

Authorized Distributors Selling Product to Secondary Distributors

Authorized distributors might provide product to the secondary market in order to meet financial goals and the activity is fairly widespread. Language in contracts between IGIV manufacturers and distributors prohibits resale to other distributors. Nevertheless, three executives in distribution indicated that this does occur, although the quantity distributed in this manner is unclear.

Healthcare Providers and Pharmacies Reselling Unused Product

In certain settings, some healthcare providers might sell a portion of their IGIV allocation to a secondary distributor. In many states, wholesaler licenses are not difficult to obtain. Most states require a simple application and a fee in the range of $500 to $1,500. Further, some pharmacies can legally redistribute a small percentage of their product without a wholesaler license. Many of the manufacturers, GPOs, and distributors judged that this is a significant source of product for the secondary market.

Some of the distributors interviewed for this study have been approached by home healthcare companies that are selling IGIV. An IGIV manufacturer recently conducted its own analysis to determine how its products reached the secondary market. It found that some home healthcare companies were reselling product into the secondary market. Investigations conducted by some of the authorized distributors have reportedly had similar findings.

2.4.2.2. Utilization of the Secondary Market

The secondary market generally serves healthcare providers that need to acquire IGIV during times of limited availability. Thus, it is frequently used by physicians and other smaller providers who only need a small amount of IGIV for a few patients or who use IGIV infrequently. These healthcare providers do not use enough IGIV to require an allocation and are unable to procure the product in other

ways, such as obtaining it directly from manufacturers or on the open market from authorized distributors. The secondary market is also a source of IGIV for providers who are on allocation but cannot meet their demand with their current IGIV allocations.

The federal drug pedigree requirements mandated by the Prescription Drug Marketing Act (PDMA) of 1987 might reduce the activity in the secondary market as they require distributors to document the chain of custody for all prescription drugs.[15] Some states already have drug pedigree requirements that require providers to acquire IGIV only from those authorized distributors that can provide a pedigree back to the manufacturer.

2.4.2.3. Size of IGIV Secondary Market

There is no reliable definition or count of the number of secondary distributors. Based on the examination of some the distributors that advertise IGIV availability, some of these firms appear to be very modest in size. There also are a limited number of large companies, including firms that might have been authorized distributors in the past. Most secondary distributors do not have written agreements with IGIV manufacturers and can only acquire product on an irregular basis. Table 2-19 depicts a sample of secondary distributors we identified through Internet searches and company advertising via email or fax.

The size of the secondary market is apparently unknown, even by market participants. According to one source, approximately 15 percent of IGIV available for distribution ends up in the secondary market, with roughly two-thirds coming from secondary distributors and the remainder being resold by providers back into the market. Based on the amount of IGIV available for distribution in 2005 (approximately 28 million grams), this equals 4.2 million grams. Some manufacturers and GPOs estimate that the amount of product in these channels is much smaller. A manufacturer executive estimated that only 2 to 3 percent of product available for distribution (or 560,000 to 840,000 grams in 2005) is sold in the secondary market. Some in the industry note that the secondary market supply has dried up significantly since manufacturers reduced the number of their authorized distributors and are actively investigating how product is ending up in the secondary market.

Based on our conversations with distributors (primary and secondary) and hospital pharmacies and an examination of emails and Internet sites advertising IGIV for sale, we attempted to determine the amount of IGIV in the secondary market. Executives involved in IGIV distribution estimated that there are about five large secondary distributors that distribute anywhere from 15,000 to 50,000 grams of IGIV per month. Smaller distributors, of which there may be well over 100 according to several sources, might distribute an average of 1,000 grams of IGIV per month, with actual totals fluctuating from a single dose to several thousands of grams from one month to the next. There also are IGIV "brokers," who specialize in aligning supply and demand for the product (e.g., they may call various healthcare providers to find out who has excess IGIV or a need for IGIV) but do not hold any in their inventory. Further, our examination of company Web sites shows that some of the authorized distributors also carry a few IGIV products that they in fact are not formally authorized to distribute.

[15] Although drug pedigree requirements of the PDMA were to go into effect on January 1, 2007, a federal court in New York has recently issued an injunction that puts a stay on them. The effective date of the drug pedigree requirements have been delayed since 1999, the publication of FDA's final rule 21 CFR Part 203.

Table 2-19: Potential Product Portfolio of Secondary Distributors as Identified by ERG

Distributor	Carimune NF	Flebogamma 5%	Gamimune N	Gammagard S/D	Gammagard Liquid	Gammar-P IV	Gamunex	Iveegam EN	Octagam	Panglobulin	Polygam S/D
ABO Pharmaceuticals [a]	●	●								●	●
Atlantic Biologicals [a][b]	●	●		●	●	●	●		●		
Bell Medical	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
BioMed Plus [a]	●	●		●	●	●	●	●	●	●	●
Chapin Healthcare [a][b]	●	●				●	●		●	●	
CT International [a]	●		●	●		●	●	●		●	●
Dubin Medical [b]	●			●	●	●	●	●	●		●
eGeneral Medical, Inc. [a]	●			●						●	
General Injectables & Vaccines (GIV) [a]	●			●		●	●			●	●
Global Pharmaceutical Sourcing [a]	●		●			●			●	●	●
Gulf Coast Pharmaceuticals [b]	●	●		●	●				●	●	
Hartford Health Services [b]									●		●
Medsource Direct [a]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Nationwide Medical/Surgical [b]	●		●	●						●	●
Oncology Supply [a]	●						●		●		
Premium Health Services [a]	●		●	●						●	●
RxUSA Wholesale, Inc. [a]		●		●			●		●		
Stat Pharmaceuticals [a][b]	●	●		●	●	●	●				

NA = not available (the company Web site does not provide a breakdown by type of IGIV products offered)
[a] Based on product selection advertised on company Web site.
[b] Based on email/fax advertising of available product.

To characterize the size of the secondary market, we first assumed that the five large secondary distributors might supply conservatively 25,000 grams of IGIV to the market on a monthly basis. We further assumed that the six authorized distributors, who advertise that they sell IGIV products that they are not authorized to distribute, are also likely to distribute similar amounts. The smaller secondary distributors and brokers probably number in the hundreds, but for the purposes of this exercise, we assumed a lower range of 50 small secondary distributors and 50 brokers that respectively supply 1,000 and 500 grams of IGIV per month on average. We used lower numbers than suggested by many of our industry contacts because it is likely that a significant amount of product changes hands multiple times. Also, many secondary distributors might not have product every month. Thus, while there may be hundreds of small secondary distributors and brokers, they may all be trading and re-trading the same 1,000 grams of IGIV. As illustrated in Table 2-20, this analysis shows that close to 4 million grams of IGIV might be circulating in the secondary market in a year. This would represent over 10 percent of total distribution of IGIV in 2005, assuming no exports.

2.4.2.4. IGIV Pricing in the Secondary Market

Prices from secondary distributors are reportedly much greater than contracted prices, sometimes averaging over $100 per gram. We examined several emails/faxes from secondary distributors to healthcare providers that contained IGIV pricing. Most of these were issued in the summer or fall of 2006. Pricing and availability varied from day to day, as secondary distributors acquire product at irregular intervals (see Table 2-21).

Table 2-20: Estimate of IGIV in Secondary Market (in Grams)

Type of Entity	Number of Entities	Monthly Supply per Entity (Grams)	Total Supply per Year (Grams)
Authorized distributors	6	25,000	1,500,000
Large secondary distributors	5	25,000	1,500,000
Small secondary distributors	50	1,000	600,000
Brokers	50	500	300,000
Total	**111**	**56,000**	**3,900,000**

Source: ERG estimate

Table 2-21: Range of Pricing of IGIV in Secondary Market as of October 2006

IGIV Brand	ASP+6% (as of 2nd Quarter of 2006)	Price per Gram
Carimune NF	$44.5	$63–$137
Flebogamma 5%	$58.2	$90–$95.16
Gamimune N	$44.5	$104
Gammagard S/D	$44.5	$75–$103
Gammagard Liquid	$58.2	$75–$113
Gammar-P IV	$44.5	$79
Gamunex	$58.2	$82–$119
Octagam	$58.2	$66–$90
Panglobulin	$44.5	$258
Polygam S/D	$44.5	$94

Source: Internet advertising, October 2006

The common characteristic of these solicitations is the large fluctuations in IGIV pricing. There were also large increases in pricing when a particular brand was known to be in short supply. A pharmacy buyer noted that secondary distributors closely study market conditions that might result in a tightening of supply, such as if a lot has not been released on time or a plant is shut down for maintenance. A secondary distributor also suggested that some secondary distributors will hoard product and release it when manufacturer supply is tight.

2.4.3. Role of Other Organizations Involved in IGIV Distribution

Drug distribution in general is a fragmented market involving numerous entities playing ever-changing roles. These entities influence the allocation and movement of the products, as well as the prices healthcare providers pay for acquiring them. This section briefly discusses the role of GPOs, PBMs, and specialty pharmacies in IGIV distribution.

2.4.3.1. Group Purchasing Organizations (GPOs)

Using collective buying power, GPOs negotiate contracts with manufacturers of pharmaceuticals, biologics, medical devices, and other supplies for their members. For IGIV, these contracts can span a number of years, although many GPOs stated that the quantity allocations are renegotiated annually. Contracted pricing is usually significantly lower than open market pricing, but can increase during the year up to a preset ceiling. Manufacturers typically pay the GPO an administrative fee of approximately 3 percent of IGIV price. Each GPO has its prime distributors that are responsible for warehousing the product, distributing it to GPO members, and collecting payments. The prime distributors pay the GPO an administrative fee ranging from 0.35 to 0.75 percent of IGIV price to service the GPO's members. According to data from the Modern Healthcare 2006 Group Purchasing survey, roughly 5,000 hospitals in

the United States often belong to more than one GPO. Further, most of the large GPOs also service alternate sites, such as physician's offices, nursing homes, surgical centers, clinics, and home healthcare (see Table 2-22).

There has been some consolidation among GPOs over time. For example, VHA, Inc. and the University HealthSystem Consortium (UHC), two national health care alliances, consolidated their supply-contracting functions in 1998 and established Novation. VHA, Inc. and UHC also formed Healthcare Purchasing Partners International (HPPI) to serve health care organizations that do not belong to either VHA, Inc. or UHC alliance. Thus, both GPOs, Novation and HPPI, are owned by VHA Inc. and UHC. MedAssets owns Shared Services Healthcare and Amerinet owns AllHealth. Further, GPOs have formed strategic alliances, such as GNHYA Ventures and Premier, Inc. Innovatix is partially owned by these two GPOs.

Table 2-22: GPO Membership, 2005 and 2006

GPO	Membership Exclusions [a]	Membership Requirements [b]	Hospitals [c]		Alternate Sites [d]	
			2005	2006	2005	2006
Amerinet [e]	No	Yes	2,315	1,890	33,374	22,227
Novation [e]	No	Yes	1,631	1,671	28,488	15,090
Premier Purchasing Partners [e]	Yes	Yes	1,532	1,478	40,011	33,952
MedAssets [e]	No	Yes	1,500	1,400	25,440	21,068
Mid-Atlantic Group Network of Shared Services	No	No	950	950	12,000	11,600
Broadlane [e]	Yes	Yes	908	935	23,733	20,935
HealthCare Purchasing Partners International	No	Yes	810	797	8,800	8,273
HealthTrust Purchasing Group	Yes	Yes	797	747	987	758
Consorta [e]	Yes	Yes	367	363	2305	2,146
GNYHA Ventures	Yes	Yes	256	132	–	–
Child Health Corporation of America	Yes	Yes	33	35	2,500	2,500
Yankee Alliance	Yes	Yes	52	35	5,087	1,835
Resource Optimization and Innovation	Yes	Yes	24	24	1,395	1,375
Coordinated Healthcare Services	No	Yes	15	14	26	26
FirstChoice Cooperative	Yes	Yes	11,187			
Innovatix [e]	No	Yes	–	–	8,500	6,415
United Service Alliance	No	Yes	–	–	–	–
WBBA	No	Yes	–	–	4	4

Source: Mantone, 2006
[a] Membership excludes or limits participation in other purchasing groups.
[b] Membership required for purchasing supplies.
[c] Total number of hospitals, including shareholders and members, purchasing supplies.
[d] Alternate sites served include physician's offices, nursing homes, surgical centers, home healthcare, and clinics.
[e] The GPO provides IGIV to members.

The two largest GPOs based on IGIV purchasing volume are Novation and Premier Purchasing Partners. The GPO marketplace is, however, very competitive where GPOs compete for market share. When a member hospital moves from one GPO to another, the IGIV allocation of the member typically does not move to the new GPO. As noted by GPOs, however, the IGIV allocation left behind by a leaving member is typically absorbed by other members on the GPO's waiting list for IGIV.

GPOs employ different IGIV allocation models. Most allocations are based on historical IGIV usage patterns. Thus, when the allocated grams of IGIV are not all purchased by a member, future allocations could be lowered. Other GPOs use programs that allow members to use only what they need

and transfer excess IGIV to other members. Historical use is still a factor in these programs, but inability to purchase all of the allocated IGIV does not necessarily lead to reductions in future allocations. Further, if a member needs more IGIV in a particular period, this need can potentially be accommodated. Thus, the distribution of IGIV depends somewhat on the type of allocation model used by the GPO.

2.4.3.2. Pharmacy Benefit Managers (PBMs)

PBMs administer the prescription drug part of health insurance plans on behalf of plan sponsors, such as self-insured employers, insurance companies, and HMOs. Their main function is to control costs and administer drug benefit programs for employers and health insurers (ERG, 2001).

The development of PBMs in the United States coincides with the emergence of prescription drug benefits in healthcare plans in the 1970s and 1980s. The precursors of PBMs include pharmacy claims processors and mail-order pharmacies. While PBMs continue to provide pharmacy claims processing and mail-order pharmacy services to their customers, many now provide additional services, including:

- Price negotiations with drug manufacturers.
- Development of pharmacy networks.
- Formulary management.
- Prospective and retrospective drug utilization reviews (DURs).
- Generic drug substitution.
- Patient compliance and education.
- Disease management programs.

The three largest PBMs (Caremark, Express Scripts, and Medco) manage the prescription drug benefit for the majority of covered patients in the United States, with numerous smaller players managing the remainder (Suchanek, 2005).

Specialty pharmaceutical management, such as that for IGIV, is a relatively new but growing area for PBMs. Many traditional PBMs have recently acquired specialty pharmacies and have developed specialty pharmacy solutions to address the issues unique to these products. Examples of recent acquisitions include Medco's acquisition of Accredo Health (a home infusion company) and Express Scripts' acquisition of Priority Healthcare (another home infusion company).

The increased use and high cost of specialty drugs is creating a sense of urgency for health plans to find new and better ways to manage them. Traditionally, specialty drugs have been managed as a medical benefit and many insurance plans still do so. However, some plans have started moving specialty pharmaceuticals over to the pharmacy benefit. Moving the benefit over to the pharmacy allows PBMs to take a role in specialty pharmacy management, such as containing costs and providing services to help in managing patients.

2.4.3.3. Specialty Pharmacies

Specialty pharmacies have been used in the past 20 years by payers to manage the high cost of injectable biopharmaceuticals, such as IGIV. Specialty pharmacies acquire products directly from the manufacturer or an authorized distributor and also receive allocations of IGIV under GPO contracts. Along with delivery of the drug, it is typical for these pharmacies to provide services such as refrigerated

delivery, billing and reimbursement assistance, clinical management and support, utilization review, and patient education, as well as any supplies needed to administer the drug. These services are typically not provided by traditional retail pharmacies.

It is difficult to precisely define specialty pharmacies as a group, because they have diverse operating structures, business models, and service offerings. They emerged from several sectors, including pharmaceutical service organizations, mail order pharmacies, disease management companies, and wholesale distributors. Thus, each specialty pharmacy defines the specialty pharmacy sector based on its specific capabilities, such as experience in infusion industry and specialty infusion, retail pharmacy or mail-order pharmacy expertise, whole distribution, and PBM skills (Smith, 2006). The traditional specialty pharmacy model is the supply and distribution of specialty drugs, such as IGIV. However, due to a number of mergers, acquisitions, and partnerships in recent years, specialty pharmacy now covers various classes of trade along the supply chain between the distribution of the product and its administration to the end user.

Although in the minority, a number of specialty pharmacies operate solely on a distribution model. These specialty pharmacies are independent operations that dispense specialty pharmaceuticals to other distributors, providers, or patients. Many of these have recently been acquired by companies further down the supply chain, such as PBMs and home infusion companies that are expanding their businesses in the specialty pharmacy market. At the other end of the spectrum are a large number of specialty pharmacies that combine direct-to-patient specialty drug shipments with home infusion services, a niche of the market called specialty infusion. Many specialty pharmacies also fall in between these two extremes. Most notably, a number of large PBMs have aligned themselves in the market by acquiring other specialty pharmacy companies, including home infusion companies and distributors. Chain pharmacies, such as CVS PharmaCare and Walgreens Specialty Services, have also recently entered the industry, but their use of IGIV appears to be limited.

2.4.5. IGIV Distribution Models

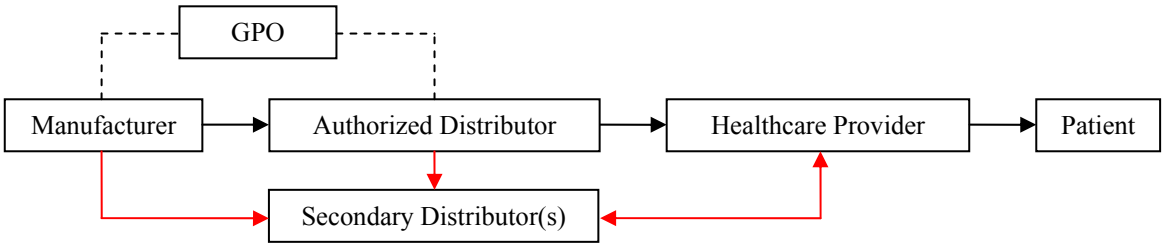
The distribution of IGIV can be categorized into three general groups: indirect sales, direct sales, and specialty pharmacy sales. Indirect sales represent sales from manufacturers to distributors. Direct sales are those that are direct from the manufacturer to the healthcare provider. Specialty pharmacy sales are a hybrid of direct and indirect sales depending on the specialty pharmacy characteristics. Each of these models is described further below.

2.4.5.1. Indirect Sales

Most IGIV is distributed through contracts that GPOs have with manufacturers. Figure 2-8 illustrates this distribution channel. Manufacturers with GPO contracts noted that more than three-quarters of their product is allocated to GPOs, whose membership consists of hospitals and alternate care sites, such as home infusion companies, clinics, surgical centers, and physician's offices. GPOs negotiate IGIV allocations and prices with manufacturers for their members but do not take ownership of the product. As discussed previously in Section 2.4.3.1, GPOs have prime distributors that are responsible for warehousing the product, distributing it to GPO members, and collecting payments. IGIV sold in this manner is typically referred to as being "encumbered."

Sales to authorized distributors without GPO contracts, i.e., open market sales, constitute another form of indirect sales. IGIV product sold in this manner from manufacturers to distributors is typically referred to as being "unencumbered." Similar to encumbered product contracts, the contract language prohibits distributors from reselling the product to any entity other than healthcare providers. Some of the contracts also cap the amount the distributor can mark up the product.

Figure 2-8: Indirect Sales Model

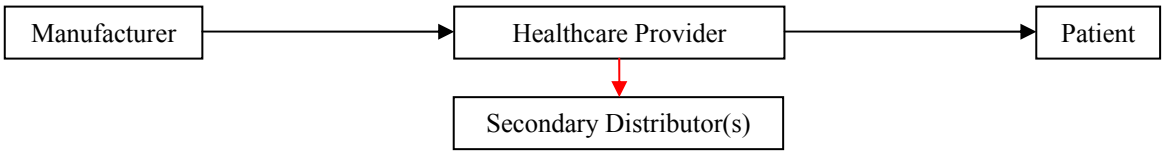


As discussed previously in Section 2.4.2, secondary distributors are not authorized by manufacturers to distribute IGIV. However, based on our conversations with industry, this market does exist and is supplied by healthcare providers and to some degree by manufacturers and authorized distributors. The red arrows in Figure 2-8 show the flow of IGIV in this secondary market. The flow of the product from healthcare provider to the secondary distributor, as well as among multiple secondary distributors is of great concern as IGIV requires careful handling during transport. For example, the liquid formulations have to remain refrigerated to maintain quality and safety.

2.4.5.2. Direct Sales

As Figure 2-9 shows, IGIV manufacturers also sell direct to healthcare providers, including university teaching hospitals, physician's offices, infusion suites, and home infusion companies. This represents a smaller portion of their total sales.

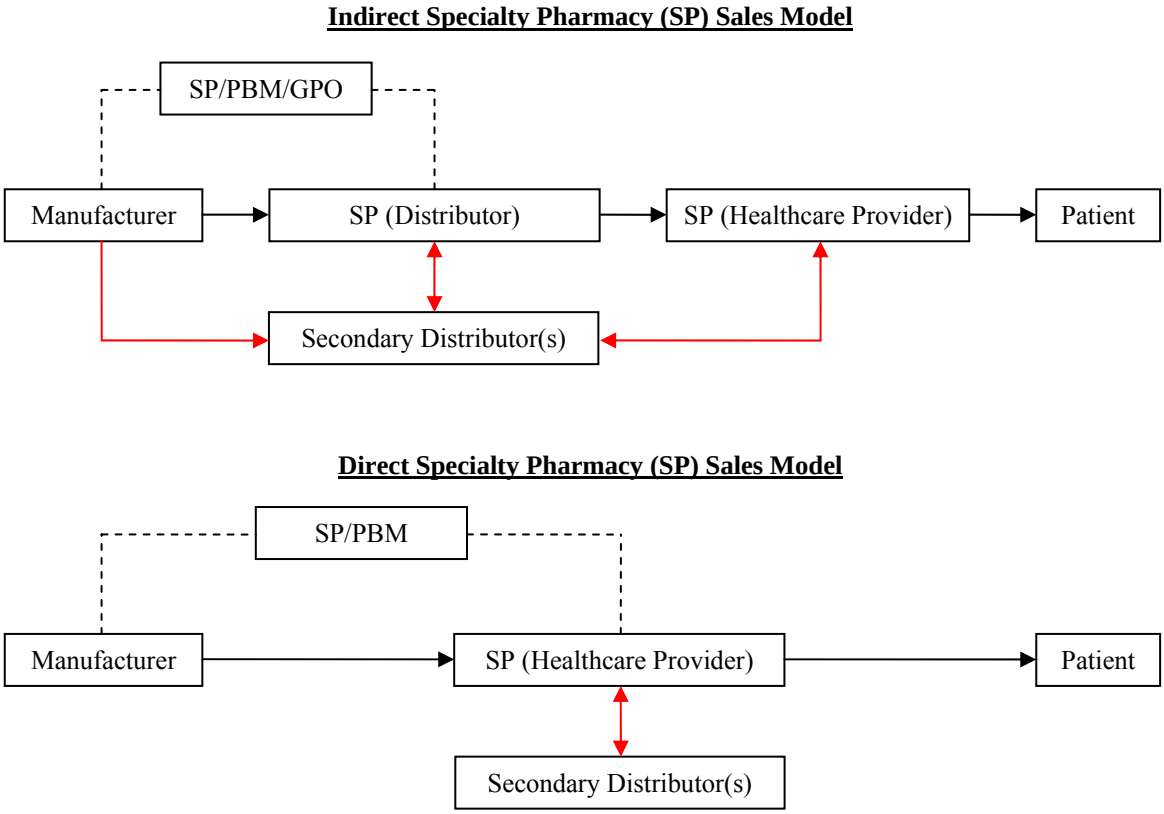
Figure 2-9: Direct Sales Model



2.4.5.3. IGIV Sales to Specialty Pharmacies

Specialty pharmacies present a complicating factor in the two models above. As noted in the previous section, many specialty pharmacies cover various classes of trade and thus can have multiple roles in distribution. Further, some specialty pharmacies may work with or function as PBMs for beneficial pricing, adjudication, and other services. As shown in an alternate version of the indirect sales model below in Figure 2-10, specialty pharmacies can act as distributors, PBMs, healthcare providers, or a combination of the three. For example, home infusion companies that function as specialty pharmacies can procure product via GPO contracts or through direct contracts with IGIV manufacturers. Specialty pharmacies can also serve solely as distributors of IGIV to healthcare providers. Alternatively, companies, such as Medco, can fulfill both of these roles. An alternate version of the direct sales model also reflects the potential role of the specialty pharmacy as a PBM and/or healthcare provider while interfacing directly with the manufacturer.

Figure 2-10: Specialty Pharmacy Sales Model



3. IGIV DEMAND

This section examines IGIV demand and utilization patterns. Section 3.1 presents the data sources used in this part of the analysis. Section 3.2 summarizes the relative strengths and weaknesses of our methodology. IGIV use, both on- and off-label uses, is described in Section 3.3. That section also delineates the various diseases currently treated by IGIV. Section 3.4 describes how IGIV is administered to patients, including typical dosages and frequency of infusions by indication. The section also provides a breakdown of sites of service for IGIV infusions. Section 3.5 discusses reported side affects and adverse reactions to IGIV infusions. The section concludes with an overview of recent IGIV demand levels and projected demand growth.

3.1 DATA SOURCES

Principal data sources for this section include peer-reviewed medical literature, data provided by the Centers for Medicare and Medicaid Services (CMS), private surveys of patients, physicians, and other healthcare providers, and discussions we conducted with patient advocacy groups, GPOs and various healthcare providers.

3.1.1. Centers for Medicare and Medicaid Services (CMS) Data on Medicare Part B Reimbursement

The Centers for Medicare and Medicaid Services (CMS) provided data on Medicare Part B reimbursements by disease category for physician's offices and hospitals for 2004 and 2005. For each principal diagnosis code, the data fields included allowed charges (in dollars), allowed units of service, estimated grams allowed by HCPCS code, and estimated total grams allowed per diagnosis code. Due to identified irregularities in the data reported from Florida, CMS reported the figures with and without Florida data. Because Florida data have been erratic and could not be interpreted for this compilation, we only used the data set that excluded Florida data for this analysis in this report.

3.1.2. Private Surveys of IGIV Usage

We used a number of private surveys conducted by the Immune Deficiency Foundation (IDF), a patient advocacy group, and the American Society of Clinical Oncologists (ASCO), a medical group. In utilizing these private survey results, we were cognizant of sample sizes, survey distribution techniques, statistical significance of findings, and sample representativeness. Although IDF represents a particular point of view (mainly, that of primary immunodeficiency patients), we used their survey results because (1) the statistics are relevant to the topic at hand (typically one with few directly relevant sources of data), and (2) the data appear reliable. We principally used these survey results for descriptive purposes and did not draw any conclusions based on precise findings from any individual survey.

3.1.2.1. Immune Deficiency Foundation (IDF) Surveys

IDF has described its methodologies in several surveys published over the last four years. The surveys are designed to track patient experiences and problems in obtaining medical care. The sample for the patient survey is drawn from IDF's database of primary immunodeficiency (PI) patients. IDF mailed the survey to a random sample of approximately 3,000 households from this database. Additionally, the survey was also sent to a supplemental sample of 135 households believed to include PI patients on Medicare to ensure a sufficient number of responses from Medicare patients to allow analysis of this key segment separately. The questionnaire instructions requested that the survey questions be completed by

either the patient or, for children or those unable to fill it out, the patient's caregiver. IDF has reported receiving 1,009 PI patient responses to its survey. After accounting for bad addresses and deceased patients, this corresponds to a 35 percent response rate.

IDF has also conducted two surveys of physicians. The first set of results was published in 2005. The sample for that survey was drawn from IDF's database of 558 physicians who reported having PI patients in a 2003 survey of physicians. There were 248 responses to IDF's physician survey corresponding to a 44.4 percent response rate.

The second physician survey was conducted in conjunction with the American Academy of Allergy, Asthma and Immunology (AAAAI) and published in 2007. A total of 230 physicians filled out the survey and roughly 7 out of 10 physicians were treating primary immune deficiency disease patients. Overall, IDF received data from 152 physicians treating 2,388 patients with IGIV. The physician survey provides timely information on the physicians' experiences in obtaining IGIV and in treating patients.

IDF also surveyed 310 hospital pharmacy directors of hospitals using IGIV and selected numbers of other pharmacies who are not or who discontinued use. The survey calls were made primarily during October, 2006. This survey covered a number of questions on price and availability of IGIV. This survey is especially timely for this study and help to describe hospital responses to the Medicare reimbursement changes during 2006.

Overall, the IDF surveys convey useful information about the status and condition of the PI patient community. The results do not necessarily represent conditions for other patients or healthcare providers regarding their use of IGIV. We have not attempted to extrapolate the IDF information to other patient populations.

Some of the IDF surveys include subjective elements and cover questions that are not readily quantifiable. The survey format also does not lend itself readily to in depth explorations of some of the complicated questions of patient health effects. Further, some questions require judgments that are probably difficult for even physicians to make, such as the effect of IGIV access problems on patient health. Any specific issues about certain questions are described as specific survey results are presented.

3.1.2.2. American Society of Clinical Oncologists (ASCO) Survey

The ASCO survey was distributed through state society offices and society committees and made available on the ASCO Web site. Because the number of oncologists who saw the survey is unknown, it is not possible to estimate a response rate for the survey. The advertisements soliciting survey participation asked respondents to help in developing a complete and accurate picture of IGIV use. ASCO staff indicated that the oncologists least likely to participate were those who do not use IGIV in their practices (Sastry, 2006).

ASCO received 81 responses. Seventy of the respondents reported using IGIV in the previous six months. The rest represent those oncology practices that are not using the product and have presumably been unaffected by IGIV issues. Joseph Bailes, M.D., executive vice president of ASCO, described the survey effort as informal in his transmittal letter of the survey results.

We do not have independent information to confirm the breadth of information covered in the ASCO IGIV survey. We discussed IGIV issues with Dr. Bailes as part of our interviewing of healthcare providers and the specifics of the survey methodology with an ASCO staff member (Sastry, 2006). The survey represents conditions for IGIV users among clinical oncologists. We have not attempted to extrapolate the results to a larger share of the physician community. We judge that the survey has merit as a snapshot of conditions for one group of healthcare providers.

3.1.3. Other Data

In addition to the above data sources, we also used peer-reviewed medical literature to characterize IGIV use, potential adverse effects of IGIV use, and the range of indications treated or potentially treated with IGIV. It should be noted that we only used specific technical findings from a few articles – for example, we quote several articles' findings on the patterns of adverse events for IGIV use – and we used those articles descriptively, without evaluating or critiquing their medical findings.

Our analysis in this section also draws from discussions we had with patient advocacy groups, GPOs, physicians and other healthcare providers, and comments received during the town hall meeting held on September 28, 2006, in Crystal City, Virginia. These interviews mainly sought further insight into IGIV demand and its growth potential. We selectively used the information from these discussions to draw general conclusions.

3.2. STRENGTHS AND LIMITATIONS OF THE DEMAND ANALYSIS

The demand analysis assembles information from a wide variety of sources. Its strengths include the following:

- The analysis utilizes private and public data sources and draws from a wide body of medical literature.
- Although we have only been able to interview a small number of GPOs, physicians, and various healthcare providers due to OMB guidelines, the individuals we interviewed presented mostly converging opinions on IGIV demand. This strengthens the generalizability of our conclusions despite the fact that they are not drawn from surveys designed to generate statistically reliable estimates.

The weaknesses of the demand analysis include core characteristics of the measurement problems posed in this type of study and several areas of the methodology.

- We have not conducted our own surveys designed to generate statistically reliable estimates. In numerous areas, such as the availability of IGIV therapy, additional and recent survey information would be useful. Nevertheless, some other survey efforts became available late in the study and have been used, as appropriate.
- Because historical market outcomes indicate only the intersection of supply and demand, we cannot observe the demand curve per se. Further, there are no objective means to measure the suppressed demand for IGIV caused by hospital efforts to limit prescribing of this product.

3.3. IGIV USE

The human immune system produces immune globulins that attack viruses and bacteria, thereby preventing infections. People with PI produce too little of these antibodies or have abnormalities in the development or maturation of immune responses, making them susceptible to infections. Other patients, such as cancer patients undergoing chemotherapy, can have weakened immune systems, which compromise their ability to fight infections. Infusions of Ig can substitute for the body's normal immunoglobulin production and help keep these patients healthy.

3.3.1. On- and Off-Label Uses

3.3.1.1. On-Label Uses

In 1981, the U.S. Food and Drug Administration (FDA) approved the first IGIV product to treat PI (Knezevic-Maramica and Kruskall, 2003). Today there are six approved medical indications for the use of IGIV products. Table 3-1 lists the FDA-approved uses for IGIV products. (The IGIV products themselves are enumerated above in Table 2-5.) The approved uses are called "on-label."

3.3.1.2. Off-Label Uses

Medical evidence supports use of IGIV for numerous off-label uses. Under the auspices of The American Academy of Allergy, Asthma, and Immunology (AAAAI), Dr. Jordan Orange and a group of doctors reviewed the medical literature to summarize the evidence supporting use of IGIV therapies for on- and off-label uses (Orange et al., 2006). Table 3-2 identifies the likely benefit of IGIV therapy for diseases other than the primary and secondary immunodeficiencies. Besides the on-label uses, Orange et al. (2006) examined data on IGIV effectiveness for autoimmune, infections and infection-related diseases, neuroimmunological and some miscellaneous uses. Orange et al. (2006) do not address all of the possible IGIV off-label uses. For example, they do not address some of the most recent proposed uses, including use as a therapy for Alzheimer's. They also do not consider or compare possible alternative therapies.

Table 3-1: FDA-Approved Indications for IGIV Products

No. of FDA-Licensed Products	Disease State	Indication
11	Primary immunodeficiency disease or primary humoral immunodeficiency	Indicated for the treatment of primary immunodeficiency states or to increase circulating antibody levels in primary immunodeficiency diseases or for replacement therapy of primary immunodeficiency when severe impairment of antibody-forming capacity has been shown.
5	Idiopathic thrombocytopenic Purpura	Indicated when a rapid increase in platelet count is needed to prevent bleeding, control bleeding, or both in idiopathic thrombocytopenic purpura or to allow a patient with idiopathic thrombocytopenic purpura to undergo surgery
3	Kawasaki disease	Indicated for the prevention of coronary artery aneurysms associated with Kawasaki disease
2	B-cell chronic lymphocytic leukemia	Indicated for the prevention of bacterial infections in patients with hypogammaglobulinemia, recurrent bacterial infections, or both associated with B-cell chronic lymphocytic leukemia
1	HIV infection	Indicated for pediatric patients with HIV infection to decrease the frequency of serious and minor bacterial infections and the frequency of hospitalization and increase time free of serious bacterial infection
1	Bone marrow transplantation	Indicated for bone marrow transplant recipients $\geq$ 20 years of age to decrease the risk of septicemia and other infections, interstitial pneumonia of infectious or idiopathic causes, and acute graft-versus-host disease after transplantation

Source: Orange et al., 2006

An increasing number of off-label uses are contributing to the growing demand for IGIV (DHHS, 2005; Kuhn, 2006). Various articles refer to the diverse and expanding number of off-label uses, with

citations ranging from 50 to over 100 off-label uses. In 2002, a Canadian panel review of medical literature found over 150 different clinical uses of IGIV (CBS, 2002).

Table 3-2: Off-label Use of IGIV by Disease Classification and by Disease

Benefit	Disease	Strength of Recommendation [a]
Autoimmune Diseases		
Definitely beneficial	Graves ophthalmopathy	A – at least one randomized controlled study
	Idiopathic thrombocytopenic purpura	
Probably beneficial	Dermatomyositis and polymyositis	B – at least one controlled trial without randomization
	Autoimmune uveitis	
Might provide benefit	Severe rheumatoid arthritis	B – at least one type of quasi-experimental study
	Autoimmune diabetes mellitus	
	Posttransfusion purpura	C – based on non-experimental study or extrapolation
	Vasculitides and antineutrophil antibody syndromes	D – Based on expert opinion or extrapolated data
	Autoimmune neutropenia	
	Autoimmune hemolytic anemia	
	Autoimmune hemophilia	
	Systemic lupus erythematosus	
	Fetomaternal alloimmune thrombocytopenia	
	Neonatal isoimmune hemolytic jaundice	
Unlikely to be beneficial	Inclusion body myositis	B – at least one type of quasi-experimental study
	Antiphospholipid antibody syndrome in pregnancy	D – Based on expert opinion or extrapolated data
Infectious and Infection-Related Diseases		
Definitely beneficial	Kawasaki disease	A – at least one randomized controlled study
	Cytomegalovirus-induced pneumonitis in solid organ transplants	
Probably beneficial	Neonatal sepsis	
	Rotaviral enterocolitis	
	Bacterial infections in lymphoproliferative diseases	B – at least one randomized controlled study
	Staphylococcal toxic shock	C – based on non-experimental study or extrapolation
	Enteroviral meningoencephalitis	
Might provide benefit	Postoperative sepsis	
	RSV lower respiratory tract infection	
	Pseudomembranous colitis	
	Campylobacter species–induced enteritis	
Unlikely to be beneficial	Chronic fatigue syndrome	A – at least one randomized controlled study
	Acute rheumatic fever	B – at least one type of quasi-experimental study
	Viral load in HIV infection	
Neuroimmunologic Disorders		
Definitely beneficial	Guillain-Barré syndrome	A – meta-analysis of randomized controlled studies
	Chronic inflammatory demyelinating polyneuropathy	
	Multifocal motor neuropathy	
Probably beneficial	Lambert-Eaton myasthenic syndrome	A – at least one randomized controlled study
	IgM antimyelin-associated glycoprotein paraprotein–associated peripheral neuropathy	
	Stiff-man syndrome	
	Myasthenia gravis	B – at least one controlled trial without randomization

Benefit	Disease	Strength of Recommendation [a]
Might provide benefit	Monoclonal gammopathy multiple sclerosis	A – meta-analysis of randomized controlled studies
	Intractable childhood epilepsy	
	Rasmussen syndrome	B – at least one type of quasi-experimental study
	Acute disseminated encephalomyelitis	C – based on non-experimental study or extrapolation
	HTLV-1–associated myelopathy	
	Cerebral infarctions with antiphospholipid antibodies	
	Demyelinative brain stem encephalitis	
	Lumbosacral or brachial plexitis	
	Paraproteinemic neuropathy	
	Opsoclonus myoclonus	
	Postinfectious cerebellar ataxia	D – based on non-experimental study or extrapolation
	Acute idiopathic dysautonomia	
Unlikely to be beneficial	Demyelinating neuropathy associated with monoclonal IgM	A – at least one randomized controlled study
	Adrenoleukodystrophy	
	Amyotrophic lateral sclerosis	C – based on non-experimental study or extrapolation
	Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome	
	Paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy	
Miscellaneous Uses		
Probably beneficial	Toxic epidermal necrolysis and Stevens-Johnson syndrome	B – at least one controlled trial without randomization
Might provide benefit	Severe, persistent, high-dose, steroid-dependent asthma	A – at least one randomized controlled study
	Prevention of infection and acute GVHD after bone marrow transplantation	
	Prevention of acute humoral rejection in renal transplantation	
	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	B – at least one type of quasi-experimental study
	Delayed-pressure urticaria	
	Treatment of acute humoral rejection in renal transplantation	C – based on non-experimental study or extrapolation
	Autoimmune blistering skin diseases and manifestation of systemic diseases	
	Chronic urticaria	
	Autoimmune liver disease	
	Acute myocarditis	
Unlikely to be beneficial	Prevention of spontaneous recurrent abortions	A – at least one randomized controlled study
	Non-steroid-dependent asthma	
	Dilated cardiomyopathy	
	Prevention of chronic GVHD after bone marrow transplantation	
	Atopic dermatitis	B – at least one controlled trial without randomization
	Autistic disorders	C – based on non-experimental study or extrapolation

Source: Orange et al., 2006
[a] Article authors classified the strength of recommendation as "A" (highest), "B," "C," or "D" (lowest).

While some off-label uses lack evidence of medical effectiveness, others are well supported by medical data. Thus, the off-label characteristic is a weak indicator of a particular use's medical appropriateness. Manufacturers often have reasons not to seek wider labeling indications. In general, they have little incentive to perform new clinical trials and to seek new labeling indications when off-label

uses are occurring anyway. Clinical trials are expensive to perform and off-label prescribing of products is legal. Further, some off-label uses are for rare conditions (e.g., pemphigus) so the affected population is small and manufacturers would realize little additional sales if such new labeling indications were added.

Overall, the literature on many IGIV uses is not considered to be well developed. Several physicians commented on the paucity of (1) good evidence on IGIV efficacy and (2) the lack of long-term studies for many treatment areas. Some of the supporting evidence for many IGIV therapies comes only from small studies published in second-tier medical journals. Further, the optimal medical treatments in some of the areas where IGIV is used remain quite uncertain. Given some considerable difficulty in diagnosis for some conditions, IGIV might be given as part of the diagnostic process, i.e., to see how the patient responds. An immunologist also noted that many initial positive patient responses are somewhat misleading and do not reflect any long-term improvement in clinical conditions. In general, some physicians judge that other physicians are over-prescribing the product.

Some physicians noted that there are numerous alternative treatments for many of these conditions. One neurologist, for example, judged that there are alternative treatments for most of his patients. Other physicians noted the considerable uncertainty about how to treat some of the conditions. Others commented that certain neurological conditions are extremely difficult to diagnose and that some experimentation with IGIV and other therapies is part of the diagnostic process. This and other physicians commented that IGIV can generate a positive patient response without necessarily changing the underlying condition or improving the long-term clinical outlook. For example, the drug will provide an immunoregulatory response that will help auto-immune diseases in the short-run. The long-term efficacy of the therapy, however, might not be established. Additionally some on-label uses are outdated or shown by clinical trials not to be cost-effective (Darabi et al., 2006). For example, there is little IGIV use for HIV treatment.

The amount of off-label use has been quantified in a number of studies, which ranges from 50 to 80 percent of all IGIV use. Although no single set of published estimates appears to be definitive, a review of the studies indicates that off-label use is very substantial.

3.3.2. Diseases Treated by IGIV

3.3.2.1. Primary Immunodeficiency

The World Health Organization recognizes nearly 100 different types of PI disorders, which are caused by genetic defects in the immune system. Although diverse, PI diseases share the common feature of susceptibility to infection and result in substantial morbidity and shortened life spans (CDC, 2004). Approximately one in 10,000 people has a symptomatic case of PI with acute or chronic infections (Beers and Berkow, 2005). Some patients are able to use antibiotics and minimized exposure to infection to maintain optimal health. But for those patients with recurrent infections, IGIV is considered the standard therapy for antibody deficiencies (Cooper et al., 2003). The first U.S. use of IGIV therapy produced for PI patients appeared in 1979 (Siegel, 2003). In a 2002 study of 3,000 PI patients, 80 percent reported that they had been treated with IGIV during the course of their illness (IDF, 2003). In a majority of cases, IGIV will be a lifelong treatment provided through a monthly infusion (IDF, 2003). Plasma exchange is an alternative to IGIV, but concerns about disease transmission make it rarely used (Beers and Berkow, 2005).

3.3.2.2. Secondary Immunodeficiency

Chronic B-cell lymphocytic leukemia (CLL). Leukemia is a cancer of the bone marrow and blood. With the chronic B-cell form, the B-cells of the immune system do not function properly, which causes

CLL patients to easily catch infections. Additionally, chemotherapy and other immunosuppressive treatments used to fight CLL also reduce the patient's immune system. Infectious complications continue to be one of the major causes of morbidity and mortality in patients with CLL (Morrison, 1998). IGIV therapy is a labeled use; if administered regularly, IGIV can protect patients from recurring bacterial infections. Between 10,000 and 15,000 new cases of CLL are diagnosed each year in the United States, and about 60 percent of these patients develop hypogammaglobulinemia, which severely reduces their ability to fight infection (Griffin, 2005).

Pediatric HIV. Serious recurrent bacterial infections are a major cause of morbidity in symptomatic children with HIV (Gangakhedkar, 2001), so IGIV therapy –a labeled use – can be an appropriate treatment for children with low Ig levels or serious bacterial infections. Advances in oral HIV therapies, however, have decreased the use of IGIV (Schleis and Siegel, 2005).

3.3.2.3. Autoimmune Diseases

An autoimmune disease is one in which the body's immune system attacks its own tissues. Autoimmune disorders are classified into two types, organ-specific (directed mainly at one organ) and non-organ-specific (widely spread throughout the body). Table 3-3 lists some of the labeled and off-label uses of IGIV in treating autoimmune diseases.

Immune thrombocytopenic purpura. The autoimmune condition immune thrombocytopenic purpura (ITP), which is believed to be caused by the body's own destruction of its platelets, can lead to bleeding disorders. The number of people in the United States with ITP is estimated at approximately 200,000 (PSDA, 2006). Treatment is usually limited to patients with life-threatening bleeding or who are symptomatic with low platelet counts. The principal therapeutic options for ITP include glucocorticoids, IGIV, intravenous anti-Rho (D), and splenectomy (George et al., 1996). There does not appear to be a difference in outcome between glucocorticoids and IGIV (George et al., 1996). Although ITP treatment is a labeled IGIV use, some treatment guidelines limit IGIV to patients for whom steroids have been found ineffective. Spontaneous remission occurs in 80 percent of untreated children, but only 10 to 20 percent of adults (Newcastle, 1997). The use of IGIV therapy as part of ITP treatment began in 1981 (Siegel, 2003).

Bone marrow and stem cell transplantation. Typically IGIV is given in two sessions before and then weekly for the first 90 days after a bone marrow or stem cell transplant from another person. IGIV therapy has been shown to reduce the incidences of infection and to prevent graft versus host disease, in which the new donor cells attack the recipient's cells. Approximately 17,700 people in North America had bone marrow and other transplants in 2003 (CIBMTR, 2005).

3.3.2.4. Infectious and Infection-Related Diseases

Kawasaki disease. The only labeled condition caused by an infection is Kawasaki disease, which affects coronary arteries and usually appears in children less than 5 years old. A single dose of IGIV is usually given in conjunction with aspirin to prevent coronary aneurysms within the first 10 days of symptoms (Orange et al., 2006). The U.S. mean annual incidence in children of non-Asian descent is 10 cases per 100,000 children under 5, and 44 cases per 100,000 Asian-descent children under 5 (Ogershok and Weisse, 2005).

3.3.2.5. Neurological Diseases

According to several studies of IGIV demand (discussed later), a large share is for neurological indications. Among these, the most common usage is for chronic inflammatory demyelinating polyneuropathy (CIDP), a chronic condition closely related to Guillain-Barré syndrome. IGIV has

become "first line therapy" for CIDP, multifocal motor neuropathy, and Guillain-Barré syndrome. IGIV is also used as a secondary treatment when other treatments fail for myasthenia gravis and Lambert-Eaton myasthenic syndrome. IGIV has also been used as a treatment in a number of other neurological disorders, such as multiple sclerosis.

Guillain-Barré syndrome occurs in approximately 2 per 100,000 people per year. It may be caused by an infectious illness, which causes an immune response that negatively impacts the nerve system (Davids, 2006). Within the first two weeks of symptoms, patients are typically given either plasma exchange or IGIV therapy if they exhibit severe weakness and develop respiratory distress (Dada and Kaplan, 2004). Currently there is no clear indication of which treatment is more effective (Davids, 2006). The typical IGIV treatment is 2 grams of Ig solution per each kg of weight (g/kg) over five days. In a small percent of patients, there is a relapse that may require another IGIV treatment.

CIDP is similar to Guillain-Barré syndrome, but with chronic muscular weakness progressively increasing for more than two months. CIDP is considered uncommon, with approximately 0.5 per 100,000 children and 1.5 per 100,000 adults diagnosed (Koller et al., 2005). The current treatment is plasma exchange, IGIV, or corticosteroids. A total dose of IGIV is typically 2 g/kg divided over five days. About half the patients receiving IGIV require repeated treatments every few weeks or months to maintain remission or treat recurrences (Wiles et al., 2002).

Multifocal motor neuropathy (MMN) is another immune-related disorder that impacts motor nerves. MMN is rare, with approximately 1 in 100,000 suffering from it (Zivkovic, 2006). IGIV is the primary treatment of choice: the starting dosage is 2 g/kg over two to five days, after which most patients require a maintenance dosage of 1 to 2 g/kg every one to two months. IGIV can become ineffective after three to seven years (Zivkovic, 2006); cyclophosphamide, an immunosuppressive agent, is used when the patient does not respond to IGIV therapy. Due to cyclophosphamide's toxic side effects and lower efficacy, doctors limit its usage.

Myasthenia gravis (MG) is an antibody-mediated disorder that creates muscle weakness. The estimated annual incidence is 2 per 1,000,000 people (Shah, 2006). IGIV therapy has been used since the 1980s to reduce MG symptoms in the short term (Wiles et al., 2002). Anticholinesterase inhibitors are often considered the first type of treatment (Shah, 2006). Other patients have improvement with corticosteroids or thymectomy (Howard, 1997).

Lambert-Eaton myasthenic syndrome, which has symptoms similar to MG, affects approximately 4 per 1,000,000 people in the United States (Kleinschmidt, 2006). Approximately 60 percent of the patients have small cell lung cancer (Wiles et al., 2002). As for MG, there is no clear-cut therapy since each patient's reaction differs. Milder cases may improve with cholinesterase inhibitors. IGIV usage in the short term has been effective with an initial dose of 2 g/kg over two to five days.

Dermatomyositis and polymyositis are considered autoimmune pathologies with no obvious infective cause (Wiles et al., 2002). Each disorder has a prevalence rate of 1 per 100,000 people. The mainstay of therapy for the muscle disease is systemically administered corticosteroids. For conditions that do not improve, the use of monthly high-dose IGIV has proved to be beneficial at a level of 1 g/kg on two consecutive days monthly (Callen, 2006).

3.3.2.6. Other Uses

Other examples of off-label use fall into the following general categories:

- *Rheumatology* – adult and juvenile arthritis and other inflammatory diseases, such as systemic lupus erythematosus.

- *Hematology* – rare blood disorders, such as hemophilia, aplastic anemia, and autoimmune hemolytic anemia.
- *Obstetrics* – recurrent pregnancy losses due to anti-phospholipid syndrome and for those undergoing in vitro fertilization.
- *Neonatal care* – babies born premature may not have benefited from the transfer of Ig across the placenta.
- *Transplants* – treatment for graft versus host disease, where a body rejects an organ donation as a foreign object.
- *Pulmonary* – some severely asthmatic children have specific antibody deficiencies.

3.4. ADMINISTRATION OF IGIV

Currently, immune globulin products are principally administered intravenously. For intravenous administration, a nurse usually places a catheter in the vein. Nurses and other medical staff will monitor the patient during the infusion (Clinton et al., 2002).

In the United States, a small share of patients receive subcutaneous therapy. In January 2006, FDA approved ZLB Behring's Vivaglobin, which is a subcutaneous IGIV product. The subcutaneous product has been used for some time in Europe. The manufacturer describes the product's benefit as providing "freedom and convenience" for safe home self-administration of Ig replacement therapy (ZLB Behring, 2006b). The subcutaneous treatment may be valuable for patients who have poor venous access or who are vulnerable to adverse reactions during intravenous infusions.

Patients are also often concerned about the length of time of an infusion. IGIV with an infusion pump takes approximately 3 to 8 hours, while an IV drip requires twice as long (Vogel, 2004). Administrators have to balance the concentration and rate of infusion with a patient's tolerance. Current recommended rates are in the range of 0.03 ml/kg/min to 0.13 ml/kg/min (Gelfand, 2003). In a survey of physician's office–based infusions, 90 percent of PI patients completed their infusions within 3 hours (Martin and Hostoffer, 2006).

Rapid infusion of IGIV is a relatively new option, although none of the physicians and infusion nurses contacted for this study were employing this technique. Infusion time can be reduced from several hours to as little as 30 minutes (IDF, 2004). Patients are typically transitioned to rapid infusion over a period of 6 to 12 months. Rapid infusion improves efficiency in the infusion operation, reduces costs, and allows greater flexibility in treatment schedules. However, this protocol is appropriate only for patients who are tolerating routine infusions with few to no side effects (IDF, 2004).

An older technique for administration is intramuscular (IMIG), in which the Ig is injected deep into a muscle. This method was first available in the 1950s and continued through the 1980s as the primary administration route until modern formulations became available that allowed for IV infusion. Today IMIG is limited to specialized treatments as administration can be painful (IDF, 2004). When intramuscular therapy was used, immunodeficient patients required large and frequent doses to achieve desired serum levels. Given the difficulty and pain of administration, few patients achieved desired IgG levels (IDF, 2004).

3.4.1. Dosage and Frequency

PI patients typically receive lower doses than patients with some of the neurological indications. The usual dose of IGIV for antibody replacement is between 0.3 and 0.6 g/kg per month, delivered intravenously every two to four weeks (Orange et al., 2006). Maintenance dosing is typically 0.4 g/kg every 3 to 4 weeks. For other uses, the doses range between 0.4 g/kg per day for 5 days or a more rapid course of 1 to 2 g/kg administered in one or two days. The half-life of IGIV in the body is approximately 18 to 33 days, which is similar to that of natural Ig (Dalakas, 2004; Andrews, 2001). Thus, some indications will require monthly infusions to maintain the necessary level of immunity. More than 80 percent of PI patients have infusions every 3 to 4 weeks (IDF, 2003; Martin and Hostoffer, 2006). Tables 3-3 and 3-4 list some of the recommended dosages and frequencies of IGIV therapy.

Table 3-3: Typical IGIV Dosage and Frequency by Indication

Indication	Dosage	Frequency
Primary immunodeficiency	0.1 to 0.4 g/kg	2–4 weeks, often for lifetime
Kawasaki disease	2 g/kg over 10 hours or 0.4 kg/day for 4 days	Once within the first 10 days of symptoms
Idiopathic thrombocytopenic purpura	0.4 kg/day for 5 days 0.4 g/kg	In response to episodes of active bleeding Maintenance dose, 2–4 weeks
Bone marrow transport	0.5 g/kg per day	Days 7 and 2 before transplant; day 6 after transplant; weekly intervals thereafter until day 90
Chronic lymphocytic leukemia, pediatric HIV	0.4 g/kg	Monthly

Sources: Newcastle, 1997; Orange et al., 2006

Table 3-4: Association of British Neurologists' Predicted IGIV Use

Indication	Frequency in Population	IGIV Dosage and Frequency	Proportion of Cases Treated with IGIV
Guillain-Barré syndrome	2:100,000 per year	0.4 g/kg for 5 days; Occasionally a second course	Most
Chronic inflammatory demyelinating polyradiculoneuropathy	5:100,000	Initial: 0.4 g/kg for 5 days Monthly: 0.6 g/kg per day	<50%
Multifocal motor neuropathy	1:100,000	Initial: 0.4 g/kg for 5 days Monthly: 0.6 g/kg per day	At least 50%
Myasthenia gravis	14:100,000	For exacerbations: 0.5 g/kg for 3 days	Rarely

Source: ABN, 2005

3.4.2. Location of Administration

Patients receive IGIV in varied environments including:

- A hospital inpatient setting.
- A hospital outpatient setting.
- A doctor's office.
- At home.

In most cases (87 percent), nurses administer the IGIV (IDF, 2003). Since 2005, there has been considerable discussion of where patients receive their infusions. As an indicator of conditions prior to the changes in Medicare reimbursement implemented in 2005 and 2006, we reviewed an IDF survey conducted in 2002 of PI patients (IDF, 2003). That survey, as represented in Table 3-5, showed patients receiving IGIV therapy in various locations. Home infusions were the most common, at 41 percent of the total non-blank responses. A later discussion reassesses the distribution of infusion locations in light of recent changes to Medicare reimbursement rates.

Table 3-5: IGIV Treatment Location for PI Patients

IGIV Treatment Location	Percentage of PI Patients
Doctor's office	12%
Home	41%
Hospital	30%
Infusion suites	11%
Multiple locations	1%
Other	5%
Total	100%

Source: IDF, 2003

In a study funded by ZLB Behring, more than 90 percent of patients preferred home IGIV treatment (Nicolay et al., 2006). A survey with PI patients who receive infusions in their doctor's office found that 97 percent were satisfied with their service (Martin and Hostoffer, 2006).

For patients motivated for self-administration at home, most guidelines suggest that at least their first two infusions be conducted at a medical facility (e.g., hospital, physician's office) because adverse reactions most often occur during the initial treatments (Ochs, 2005). During any IGIV administration at home, another person should be present in case of an adverse reaction. Patients are required to maintain infusion records and to be trained on technique and infusion site selection and rotation.

3.5. SIDE EFFECTS AND ADVERSE REACTIONS

A number of articles provide estimates of the frequency of adverse events from IGIV administration. The estimates, however, are applicable to the specific situation and patients studied. Also, few studies give insight into whether IGIV brand switches, which are reported to be fairly common recently, contribute to an increase in adverse events.

While IGIV therapy is generally considered safe, the cause and precise incidence of mild to severe adverse events is not known (Durandy et al., 2005). Manufacturers report an adverse incidence rate per patient of between 1 and 15 percent during the clinical trials. An IDF survey indicates that 29 percent of PI patients had an adverse reaction to IGIV in the past year (IDF, 2003). IDF also noted that 34 percent of patients said their adverse reactions had occurred when they were trying a product for the first time (IDF, 2003). Table 3-6 lists a sample of articles that report adverse reactions from IGIV. In these articles, the range of adverse events is between 0.8 percent and 50 percent for mild-moderate effects. The low end of the range is a survey of patients who had been given at least six previous IGIV infusions (Brennan et al., 2003), while the high end of the range is for patients' first infusion, which was given at a rapid rate (Sekul et al., 1994). In that study, an additional 11 percent of patients had severe side effects.

Mild reactions to IGIV therapy include headache, flushing, lower back pain, myalgia, nausea, chills, and abdominal pain (Bleeker et al., 2000). Headache is the most common complaint (Gelfand, 2006; Dalakas, 2004; IDF, 2003). Moderate reactions include bronchospasm, chest pain, and worsening of

mild symptoms. Most reactions are mild and self-limited (Kleinman, 2002). Fatigue, fever, or nausea may occur after infusion and may last as long as 24 hours. IDF also advises that mild reactions can occur up to 48 hours post-transfusion (IDF, 2004).

Common factors associated with these reactions are 1) too fast an infusion rate (Bleeker et al., 2000; IDF, 2004), 2) lapses between treatments, or 3) switching to another IGIV brand (Kleinman, 2002). Comparison of adverse reactions among different IGIV products is difficult to establish given the variation in the recipients' situation, such as diagnosis, infusion rate, and cumulative IGIV dosage.

Table 3-6: Sample of Research Regarding Adverse Events from IGIV

Patient Type	# of Infusions	Count (Percent)			References
		Mild	Moderate	Severe	
Children with PI	1,231	131 (11%)	19 (2%)	2 (0.2%)	Aghamohammadi et al., 2004
Patients with neuromuscular diseases, first infusion, rapid rate	54	27 (50%)		6 (11%) [a]	Sekul et al., 1994
PI, self-infusing at home, having ≥ 6 infusions	13,508	91 (0.7%)	20 (0.1%) [b]	0 (0.0%)	Brennan et al., 2003
Adults with neurological autoimmune disorder, 16% with previous IGIV therapy	341	Headache (30%) Nausea (11%)		3 (0.9%) [c]	Stangel et al., 2003
Adults with autoimmune disorder, 47% with previous IGIV therapy	337	30 (9%) [d]			Schmaldienst et al., 2001
Adults and children with PI, office based infusion	473	101 (21%)			Martin and Hostoffer, 2006
Experienced first demyelinating event suggestive of multiple sclerosis, age 15 or older	538 IGIV	28 (5.2%)		0 (0.0%)	Achiron et al., 2004
	431 placebo	29 (6.7%)		0 (0.0%)	

PI = primary immunodeficiency
[a] Patients developed aseptic meningitis.
[b] One patient dropped out after 11 adverse events.
[c] One patient had an allergic reaction, another patient developed a thrombosis, and a third patient experienced intense retrosternal pressure sensation.
[d] Four patients dropped out due to frequency and severity of adverse effects.

Most often, symptoms occur during the first infusion (Orange et al., 2006) and can be minimized with slower infusion rates or the use of medication to offset the symptoms (Gelfand, 2006; Ochs, 2005). Patients generally develop tolerance to these side effects; if not, another IGIV brand might be better tolerated (Martin and Hostoffer, 2006).

Rarely, patients have severe reactions, such as anaphylactic reactions, renal failure, and aseptic meningitis. Many of these side effects have occurred in patients who have significant, underlying risk factors (e.g., hypertension, diabetes, previous stroke, IgA deficiency, over age 65) (Hamrock, 2006; Kleinman, 2002).

Infusion administrators are advised to review the patient inserts with each product to identify potential adverse reactions and the patients at greatest risk. Also, close monitoring by trained personnel at all infusions is recommended for early detection of adverse events.

Patient and physician comments (ERG, 2006) also suggest that some adverse reactions are fairly long-lasting (i.e., more than a day in duration) and can even be enough to discourage patients from

receiving treatments. ERG reviewed two articles that referenced dropout rates of 16 percent of 88 patients (Kleinman, 2002) and 24 percent of 18 patients (Schmaldienst et al., 2001) due to adverse reactions. Kleinman suggests that this may be related to the higher IGIV therapy dosage and the fact that the patients were older and with severe diseases.

Recent issues of patient access, as discussed further below, indicate that some patients have received a number of different IGIV brands in the last few years. It is generally believed that adverse reactions are increased when patients are shifted among brands, although randomized controlled studies to verify this are not available (Kleinman, 2002). An IDF survey of PI patients indicates that 39 percent of patients felt that they tolerated certain IGIV products better than others (IDF, 2003). Eleven percent of these patients have refused a product and another 7 percent delayed their infusion due to tolerability concerns. The survey also found that 34 percent of all infusion related adverse events occur in the context of a product change (IDF, 2003).

Adverse reactions among patients are also possible after changes to manufacturing processes. A study documented the effect of such changes in IGIV manufacturing in Australia and New Zealand (Ameratunga et al., 2004). CSL changed its manufacturing process for the IGIV product Intragam. When the new product, Intragam P, was given to patients, seven of 49 of them had adverse reactions. None of the patients had experienced adverse reactions with the previous Intragam infusions. The precise medical cause of the reactions was not clear.

Trends in IGIV product development suggest that adverse events might decline in the future. Newer products will not have the sugar levels found in current products, reducing the likelihood of renal failures. Also, an immunologist with numerous IGIV patients forecast the phasing out of lyophilized products could standardize the products given and reduce adverse events.

3.6. CHARACTERISTICS OF RECENT DEMAND LEVELS AND DEMAND GROWTH

3.6.1. Change in Demand Resulting from New IGIV Uses

The expansion in the number of recognized uses for IGIV has increased demand for the product, especially in the past decade. Section 2 presented summary data on sales by product by year for each of the IGIV products and showed the overall growth in usage. Many medical groups have observed that the off-label demand is a very large share of the total. For example:

- A 1999 report by the University HealthSystem Consortium, a coalition with 200 members, estimated that 58 percent of inpatient IGIV use was off-label (Andrews, 2001).
- A study of Canadian IGIV treatments during 1997 and 1999 found that 53 percent were off-label treatments (Hanna et al., 2003).
- The London Laboratory Services Group retrospectively reviewed three years (2000–2003) of IGIV utilization at two tertiary care hospitals in London, Canada. Over the three-year range, off label use of IGIV was between 81 and 86 percent (Eckert et al., 2006). (As previously noted, a hospital study would not fully represent all IGIV uses and would probably underestimate PI use, which is on-label.)

To explore the growth of IGIV uses, we reviewed the medical literature in PubMed to identify the date of the first published article regarding research on IGIV and its use for a diagnosis. During the 1980s, when IGIV products were first introduced, the therapy was used for the treatment of a number of indications. Table 3-7 presents the list derived from this literature review. The list might not indicate the precise point at which medical evidence of a beneficial use became definitive (i.e., we did not critically

review the literature for each medical indication), but it is intended to give an indication of the growth of demand over time. Thus, it displays the timing of the approximate beginnings of medical community awareness of potential benefits of IGIV use for new indications.

Table 3-7: Timeline of Early Medical Literature References Reporting Potential Value for IGIV Use for Medical Indications

Indication	Year First Published	Reference	Orange et al. Opinion of IGIV Use as Therapy
Ammaglobulinemia	1985 or before	Mease et al.	Definitely beneficial
Idiopathic thrombocytopenic purpura		Imbach et al.	Definitely beneficial
Primary immunodeficiencies		Buckley	Definitely beneficial
Aplastic anemias		Clauvel et al.	Not listed
Bone marrow transplant		Winston et al.	Might provide benefit
Chronic lymphocytic leukemia		Besa	Probably beneficial
Kawasaki disease		Johansen et al.	Definitely beneficial
Kidney transplant		Fassbinder et al.	Might provide benefit
Myasthenia gravis		Fateh-Moghadam et al.	Probably beneficial
Myeloma		Gordon et al.	Not listed
Pemphigus		Hunziker et al.	Might provide benefit
Prevention of infection in HIV		Silverman and Rubinstein	Probably beneficial
Rhesus isoimmunization		Berlin et al.	Not listed
Intractable childhood epilepsy	1986	Duse et al.	Might provide benefit
Prevention of neonatal sepsis	1986	von Muralt and Sidiropoulos	Probably beneficial
Guillain-Barré syndrome	1987	Ceccarelli et al.	Definitely beneficial
Rheumatoid arthritis	1987	Sany et al.	Might provide benefit
Stem cell transplant	1987	McGuire et al.	Definitely beneficial
Systemic lupus erythematosus	1988	Pahwa	Might provide benefit
Asthma	1989	Mazer et al.	Might provide benefit
Cystic fibrosis	1989	Winnie et al.	Not listed
Prevention of spontaneous abortion	1989	Mueller-Eckhardt et al.	Unlikely to be beneficial
Dermatomyositis and polymyositis	1990	Bodemer et al.	Probably beneficial
Type I diabetes	1990	Panto et al.	Might provide benefit
Churg-Strauss	1991	Hamilos and Christensen	Not listed
Multifocal motor neuropathy.	1992	Charles et al.	Definitely beneficial
Multiple sclerosis	1992	Cook et al.	Might provide benefit
Stevens-Johnson syndrome	1992	Amato et al.	Probably beneficial
Fisher syndrome	1993	Arakawa et al.	Not listed
Inclusion body myositis	1993	Soueidan and Dalakas	Unlikely to be beneficial
Sickle cell anemia	1993	Gangarossa and Lucini	Not listed
Necrotizing fascilitis	1994	Yong	Not listed
Pancreas transplant	1994	Stratta et al.	Definitely beneficial
Stiff-man syndrome	1994	Karlson et al.	Probably beneficial
Staphylococcal toxic shock	1995	Ogawa et al.	Probably beneficial
Autism	1998	Plioplys	Unlikely to be beneficial
West Nile virus	2001	Shimoni et al.	Not listed
Alzheimer's disease	2002	Dodel et al.	Not listed
Psoriasis	2002	Gurmin et al.	Not listed
Narcolepsy	2003	Lecendreux et al.	Not listed
Severe acute respiratory syndrome	2003	Chiang et al.	Not listed
Post-polio syndrome	2004	Farbu et al.	Not listed

Source: Compiled by ERG; Orange et al., 2006

We also identified whether the specific use was judged to be beneficial in the review of usage conducted by Orange et al. (2006). Of the 10 indications researched and published before 1985 that Orange et al. reviewed, for example, IGIV is thought to be beneficial. Orange et al. (2006) did not assess any of the newer IGIV uses, for which evidence has been published since 2000.

Some of the uses listed have not yet significantly affected demand but hold the potential to do so. For example, in 2006, researchers at Weill Medical College of Cornell University announced that IGIV halted the development of Alzheimer's disease. The cause of Alzheimer's disease is unknown and there is no cure (Grady, 2006). With more than 4 million people in the United States diagnosed with Alzheimer's, this small study of eight patients, with six showing maintained or improved cognition from their baseline, showed promising results. The researchers stated that larger randomized controlled trials were needed to determine the efficacy and safety of IGIV therapy on Alzheimer's patients (Barclay, 2006).

3.6.2. Use Levels by Disease Category

The aggregate U.S. use of IGIV represents the sum of IGIV treatment in the numerous disease categories described earlier. Figures on IGIV use by disease are varied and incomplete, however, making the breakdown of use by disease category uncertain. This section presents several sources of information on use by disease category. None of the individual sources are adequate to represent aggregate demand by disease, however.

The CIS published an analysis, using 2002 data from Arlington Medical Resources (AMR), of demand for IGIV in a large sample of hospitals. AMR samples hospital purchases and distributes the results for a fee. The AMR study estimate of IGIV use, summarized in Table 3-8, lists the top uses of IGIV for the AMR sample of hospitals. The data do not cover physician or home healthcare uses and cannot be considered fully representative.

According to AMR, neurological uses are among the largest uses for IGIV, with 24 percent and 32 percent of demand in the inpatient and outpatient settings, respectively. ITP patients receive 27 percent and 13 percent of the product used for inpatient and outpatient therapies, respectively.

Additional data can also be drawn from individual hospitals that surveyed their internal use of IGIV. Individual hospital perspectives are not entirely reliable for characterizing the hospital sector because an individual hospital is unlikely to have a nationally representative selection of patients needing IGIV therapy (i.e., it may have certain specialties, outpatient clinics). Also, the hospital data overestimate the share of IGIV use for disease episodes that require hospitalization and underestimate use for diseases treated with home infusion services. Nevertheless, given the lack of more authoritative aggregate statistics, the hospital data give a preliminary view of IGIV use by disease category. (Additional hospital-specific compilations are not reviewed here.)

Table 3-8 also shows results from a review of IGIV usage at Massachusetts General Hospital (a large metropolitan hospital) during 2004. The review covered 194 patients receiving IGIV; 61.9 percent of the IGIV was given to those with chronic neuropathy, such as CIDP (Darabi et al., 2006). These patients also received relatively large dosages, averaged at 530 grams per patient. In contrast, patients being treated for ITP received only 190 grams on average. This hospital maintains an IGIV usage protocol, which requires IGIV use to be approved by a physician within the Blood Transfusion Service. The authors suggest that this approval process likely decreased the amount of off-label IGIV for situations in which IGIV's efficacy has not been proven (Darabi et al., 2006).

Other hospital data have also shown neurological uses to be a relatively large component of demand. According to the review of two London Ontario hospitals of their IGIV usage, more than 57 percent was for neurological indications (Eckert et al., 2006).

Table 3-8: Estimates of Demand for IGIV by Disease Category (Percent of Total Demand)

	Massachusetts General Hospital, 2004	Arlington Medical Resources, 2002		CMS Data, 2005	
Indication	**% of Total Amount**	**Hospital Inpatient**	**Hospital Outpatient**	**Hospital Outpatient**	**Physician's Office**
Idiopathic thrombocytopenic purpura [a]	7.9	27.0	13.0	4.4	7.2
Bone marrow transplant and other hematological malignancy	6.6	NA	NA	5.9	4.8
Lymphoma leukemia [b]	NA	13.0	19.0	5.5	12.7
Primary immunodeficiency	NA	4.0	17.0	24.9	31.4
Primary hypogammaglobulinemia and common variable immunodeficiency [c]	*9.4*	*NA*	*NA*	*22.3*	*30.8*
Neurological disease	NA	24.0	32.0	43.8	32.0
Myasthenia gravis	*3.7*	*NA*	*NA*	*5.9*	*4.9*
Guillain-Barré syndrome	*3.2*	*NA*	*NA*	*2.2*	*1.7*
Chronic neuropathy (chronic inflammatory demyelinating polyradiculoneuropathy, multifocal motor neuropathy)	*61.9*	*NA*	*NA*	*25.7*	*22.7*
Dermatomyositis	2.0	NA	NA	1.6	1.0
Necrotizing fascilitis	1.5	NA	NA	< 0.1	0.0
Renal transplantation	1.0	NA	NA	0.4	0.0
Infectious disease	NA	7.0	4.0	0.6	0.5
Non-hematological cancers	N/A	5.0	5.0	1.4	1.5
Hereditary and metabolic disease	NA	5.0	1.0	NA	NA
Surgery and trauma	NA	4.0	2.0	NA	NA
Other	2.8	11.0	7.0	11.5	8.9
Total	**100.0**	**100.0**	**100.0**	**100.0**	**100.0**

Source: Darabi, 2006; CIS, 2006; CMS, 2006
NA = Not available or not reported
[a] For the purposes of this table, ITP is identified by the International Classification of Disease codes 287.3 (Primary Thrombocytopenia) and the more specific 287.31(Immune thrombocytopenic purpura), 287.30 (Primary Thrombocytopenia, unspecified), 287.33 (Congenital and hereditary thrombocytopenic purpura), and 287.39 (Other primary thrombocytopenia) when available.
[b] Acute and chronic, with and without remission
[c] Identified by International Classification of Disease code 279.0 (Deficiency of humoral immunity) and inclusive of all more specific diagnoses (279.00 - 279.09)

We also received data for Medicare reimbursements for 2004 and 2005. The CMS data describe the quantity of IGIV dispensed by principal diagnosis code, as captured in the Medicare coding system. We compiled these figures by combining the appropriate codes for each disease category. (The tabulations excluded data from Florida, whose Medicare reporting during this period appears to have been erratic and could not be interpreted for this compilation.) The CMS data indicate that among the Medicare recipients, neurological uses require the largest share of IGIV use. PI patients are not particularly numerous among the elderly and represent approximately one quarter of all demand in the CMS data. Thus, these data, while representing a fairly large share (roughly 20 percent) of IGIV patients, cannot be considered fully representative of the pattern of total U.S. demand.

In conclusion, looking at the three data sources summarized in Table 3-8, it is possible to determine that the largest areas of demand are the various neurological and primary immunodeficiency diseases. The three sources do not include home healthcare demand, and this likely produces an underestimate of the share of use for PI. As reported in IDF's 2003 survey, approximately half of PI patients receive their infusions outside a hospital or physician's office. Thus, none of the three sources, or the three sources combined, provides a completely reliable view of IGIV use by disease category.

3.6.3. Estimating the Current Shortfall in Supply

Based on our interviews with GPOs and healthcare providers, we tried to ascertain whether current IGIV supply satisfies current demand and, if not, the extent of the shortfall. The aggregate quantity of IGIV consumed annually is the only objective quantitative indicator of aggregate market size.

The true demand for IGIV is not observable. However, one can use a number of indicators to gauge the existence and extent of a supply shortfall. One such indicator of a supply shortfall is the existence of an allocation system designed to basically ration the product. As has been noted previously, IGIV has been on allocation since early 2005, with the exact dates varying by manufacturer. Under the allocation system for IGIV, healthcare institutions can typically only obtain an amount of IGIV based on the amount of IGIV they were using in 2004. Allocation is employed as a means to maintain an orderly market when supply will not satisfy demand at current prices. Many healthcare institutions are unable to obtain additional product to support new uses or increased patient populations.

GPOs and distributors reported that their healthcare customers would be able to purchase larger volumes of IGIV than are currently made available. Table 3-9 presents a brief synopsis of GPO comments regarding level of IGIV demand relative to supply. The GPO interviews indicate that supply fails to meet demand at current prices, although one GPO judged that it could just meet its members' demand.

Table 3-9: Synopsis of GPO Comments Regarding Level of IGIV Demand Relative to Supply

GPO Specific Comments
GPO maintains a waiting list of members desiring incremental IGIV supply. Their waiting list represents considerable suppressed demand.
GPO has been able to obtain enough, with no excess, to meet its members' demands. GPO works with clients to educate them on use of blood products, distributes suggested protocol (designed to limit less effective uses) through advisory committee made up of membership.
GPO needs an additional monthly allotment that represents a significant percentage of its existing allotment.
GPO cannot meet current demand of clients, cannot begin to address increases in demand.
GPO has waiting list that represents a significant percentage of its existing purchases of IGIV. The estimate might overstate its potential demand to some extent because it includes demand by healthcare providers that are joining this GPO.

It is important to note that the IGIV demand estimates by GPOs might exaggerate the actual demand for IGIV. Due to market share competition among GPOs, the combined GPO demand for IGIV might include overlapping demand for the same healthcare institution by more than one GPO. Nevertheless, the GPOs interviewed could generally distinguish the demand increases represented by new or potential new members from the demand represented by existing members. One GPO likened the situation to one in which a company might report that "same-store sales" had increased over time. We estimate that the effect of any overlapping or double-counting of demand remaining in the estimates is limited. As noted in the comments, some GPOs maintain substantial waiting lists of IGIV demand from existing members.

Table 3-10 presents the estimated gap between supply and demand, as gauged by GPOs and by a small sample of hospitals. To generate these estimates, we asked the GPOs and hospitals to estimate the incremental amount that they could purchase for their membership. The GPOs generally agreed that if they could contract for more IGIV at current prices, their membership would be eager to buy it.

Table 3-10: GPO and Hospital Estimates of IGIV Supply Shortfall

Entity	% Gap Between IGIV Supply and Demand
Weighted average of 6 GPOs	14%
Weighted average of 4 hospitals	11%

Source: ERG interviews with GPOs and hospitals

While GPOs contract for a large share of total IGIV supply, the supply is distributed through authorized and secondary channels. Thus, we also contacted large and small distributors of IGIV to get their sense of current IGIV demand relative to supply. The distributors contacted also judged that considerably more demand exists at current prices than is supplied.

The IDF survey of hospital pharmacy directors also quantified the shortfall of supply relative to demand. The survey results showed that a majority (72 percent) of hospital allocations in 2006 do not satisfy all hospital demand. For 27 percent of hospitals, the allocations fall well short of satisfying demand. IDF calculated the average shortfall among unsatisfied hospitals at 220 grams per month, although the median shortfall was substantially less, at 80 to 85 grams per month. For perspective, the distribution of hospital use of IGIV is shown in Tables 3-11 and 3-12.

Table 3-11: IDF Survey Results on How Much of Hospital Pharmacy IGIV Needs Met by GPO Allocation [a]

Response	Percentage of Respondents
All	28%
Most	45%
Some	17%
Few	5%
None	5%
(If not all) How much more IGIV per month do you need? (mean)	220 grams
(If not all) How much more IGIV per month do you need? (median)	80-85 grams

Source; IDF, 2007a

[a] Survey question: Does your allocation meet all, most, some, few, or none of your recent needs?

Because the large majority of hospitals use less than 1,000 grams per month (combining inpatient and outpatient use), and more than one-third uses less than 200 grams per month, these shortfalls in allocation are significant. IDF survey also asked hospital pharmacy directors who they purchased IGIV from during 2006. The IDF survey reported that, in addition to GPO, manufacturer, and contractual

distributor purchases, 29 percent of hospitals made purchases from non-contractual distributors and 6 percent made purchases from other unclassified sources. These purchases represented 7.5 percent of all purchases. The last two categories of purchases would represent purchases made outside the hospital allocation. Additionally, hospitals might have been able to purchase unencumbered IGIV from the authorized distributors to alleviate the shortfall. Thus, while the allocation data suggests a shortfall, the eventual outcome (i.e., whether or not IGIV beyond the allocation could be obtained), is not precisely defined in the survey results.

Table 3-12: IDF Survey Results on Grams of IGIV Dispensed in an Average Month by Hospital Pharmacies, by Inpatient and Outpatient Use

Quantity of IGIV	Outpatient Use [a]	Inpatient Use [b]
Less than 100 grams	38%	50%
100-499 grams	42%	34%
500-999 grams	8%	7%
1,000 plus grams	6%	4%
Don't know	5%	4%

Source: IDF, 2007a
[a] For outpatient use, there were 263 responses.
[b] For inpatient use, there were 278 responses.

Qualitatively, IDF concluded that hospital pharmacy directors judged, on balance, that it was becoming more difficult to obtain sufficient IGIV from GPOs (47 percent) or contractual distributors (43 percent). In contrast, only 12 percent and 9 percent said obtaining sufficient IGIV from these two routes had become easier over time.

IGIV manufacturers have consistently stated that there is no shortfall of supply relative to demand. While it is true that some IGIV is available in secondary channels, the prices at which IGIV is offered for sale are well above what healthcare providers can recover in reimbursement. The high pricing for IGIV in the secondary channel is in fact indicative of a supply shortfall. Basic economic theory suggests that the normal market response to a shortfall is higher prices. Higher prices, in turn, draw more IGIV to the market and quantity supplied increases to meet the demand (Boulis et al., 2002).

3.6.4. Forecasting Future Growth in IGIV Demand

Recent demand patterns as well as the continuing evolution of medical research suggest fairly robust future growth in demand for IGIV. IGIV sales from 2003 through 2006 reflect a growth in utilization of approximately 7 percent per year. This growth represents only the utilization that has been satisfied with existing supplies – additional, unrealized demand is not observable. As has been noted, some hospitals have imposed usage review protocols that limit the amount of IGIV prescribed. Even where formal protocols do not exist, physicians and hospitals might experience some restraint in expanding their use of IGIV. While the impact of these influences on demand is not measurable, we judge that there is a fairly sizeable suppressed demand. Thus, the observable demand growth is judged to be less than the total demand growth.

IGIV demand growth has been stimulated by findings in the medical literature on new and emerging uses for IGIV. Researchers have performed clinical trials of IGIV effectiveness for a variety of conditions. The pace of this research has been substantial and there continues to be substantial interest in a number of developing research areas. A prominent example of a growth potential is the possibility of IGIV use as a therapy for Alzheimer's disease.

IGIV also appears to have the potential for substantial growth in therapy for autoimmune diseases. Broadly speaking, some doctors have characterized the medical evidence on IGIV effectiveness in this area as uncertain. Nevertheless, doctors have also viewed the potential for productive use against autoimmune diseases as enormous and another possible engine of demand growth. One immunologist foresees a potential for exponential growth in demand in the autoimmune arena.

There is continued use and research of IGIV use in areas where the product has shown only limited effectiveness to date. For example, some physicians use IGIV to treat infertility. This use, although modest in aggregate terms, continues without any reimbursement from insurance companies.

Various IGIV market analysts have forecast continued market growth. For example, the Australian National Blood Authority has projected IGIV worldwide demand out to 2011. They estimate that worldwide demand will grow from approximately 68 million grams in 2005 to just over 100 million grams in 2011. This suggests nearly 7 percent growth per annum over this period (Turner, 2006). On the other hand, various healthcare providers and GPOs we interviewed for the study indicated a higher IGIV demand growth ranging from 10 to 15 percent.

Overall, the demand for IGIV is expected to grow at a fairly rapid rate. With the uncertainty about the value of certain current and prospective therapies, however, any quantitative estimate of rate of demand growth is highly speculative.

4. IGIV ACCESS PROBLEMS

This section examines the various IGIV access problems reported by patients and physicians. Section 4.1 presents the data sources used in this part of the analysis. Section 4.2 summarizes the relative strengths and weaknesses of our analysis. Section 4.3 characterizes the difficulties physicians, hospitals, and other healthcare providers have had with access to IGIV using the data from IDF and ASCO surveys. Section 4.4 describes the various reimbursement difficulties reported by healthcare providers. The section also examines Medicare coverage provisions for IGIV under different settings, reimbursement patterns for on- and off-label uses, and reimbursement level sufficiency. Section 4.5 summarizes the reported consequences to patients from IGIV prescription and/or administration changes. The section concludes with a discussion of company incentives for providing IGIV infusion services in light of Medicare reimbursement.

4.1. DATA SOURCES

The analysis presented here is descriptive in nature and relies on data provided by CMS, private surveys of patients, physicians, and other healthcare providers, physician and patient comments received during the town hall meeting held on September 28, 2006, in Crystal City, Virginia, and discussions with physicians, hospitals, and home infusion companies.

4.1.1. Centers for Medicare and Medicare Services (CMS) Data on Medicare Beneficiaries Receiving IGIV

CMS provided data on the number of Medicare beneficiaries receiving IGIV infusions in hospitals, physician's offices, and in the home from the first quarter of 2004 through the first quarter of 2006 by principal diagnosis code. The data were based on final action claims from CMS's National Claims History file. For analysis purposes, CMS defined the primary diagnosis as the diagnosis most frequently listed as the principal diagnosis code across all IGIV claims for an individual beneficiary in the time period of analysis. The data were based on an analysis of J1563 and J1564 codes for 2004 and the first quarter of 2005; Q9941, Q9942, Q9943, and Q9944 codes for the 2nd through 4th quarter of 2005; and J1566 and J1567 codes for 1st quarter of 2006.

4.1.2. Private Surveys of IGIV Access

We used a number of private surveys conducted by the Immune Deficiency Foundation (IDF), a patient advocacy group, the American Society of Clinical Oncologists (ASCO), a medical group, and Public Hospital Pharmacy Coalition (PHPC), an association representing 335 public and private non-profit hospitals and health systems. The IDF and ASCO surveys are the same as those described in Sections 3.1.1 and 3.1.2, and hence are not reiterated here. A description of the PHPC survey is provided below.

In February of 2006, PHPC surveyed its member hospitals and health systems and summarized its findings in a report published on October 2006. The PHPC survey asked hospitals whether they are able to obtain IGIV at all and whether they can obtain it at discounted prices. PHPC reported receiving 134 responses from its 335 member hospitals, for a response rate of 40 percent.

PHPC is an organization of public and private nonprofit hospitals and health systems in the United States. It advocates for the affordability and accessibility of pharmaceutical care for the nation's low-income and underserved populations. Therefore, the survey represents conditions for a group of public hospitals that, by their operating charters, appear particularly vulnerable to changes in Medicare

reimbursement policies or to conditions that affect indigent populations. IGIV market impacts might have disproportionate affects on these hospitals and on their patient populations, relative to the entire population of hospitals and their patient populations. Similar to the other private surveys, the PHPC survey might also incorporate a self-selection bias – hospitals that are experiencing problems may be more likely to respond to the survey on IGIV access. We lack any ability to measure this potential bias.

4.1.3. Other Data

In addition to the above data sources, we also relied on information gathered at the town hall meeting from individual patients and physicians, and discussions we conducted with GPOs, distributors, physicians, patients, hospitals, home infusion companies, and other healthcare providers. We acknowledge that the majority of this information is anecdotal and that we lack any type of control group against which to compare experiences. As such, the information must be used with caution. The extensive caveats applicable to this information are discussed further in the following sections.

4.2. STRENGTHS AND LIMITATIONS OF THE ACCESS ANALYSIS

The key strength of this analysis is its incorporation of numerous provider perspectives regarding IGIV access. We have contacted executives in most of the principal corporate participants in the IGIV market as well as a broad sampling of IGIV-using healthcare institutions, their personnel, and their patient populations. As a result, we have been presented with a wide diversity of opinions and viewpoints regarding the functioning of the IGIV market and the related reimbursement issues.

Our analysis is, however, limited because of the anecdotal nature of this information. Most of the IGIV access problems discussed in this section are from self-reported experiences of patients and physicians. We had no objective means to verify the exact nature of these reported access problems. Furthermore:

- Many of the people interviewed for this study have self-interested perspectives that might influence their opinions regarding the IGIV market and/or the adequacy of Medicare reimbursement. Having collected a variety of materials and opinions, we have some basis on which to critically assess individual pieces of information. Nevertheless, the information might contain undetected biases as well as detected ones.

- The market is rapidly evolving, as reimbursement changes and continual price changes influence economic actions. While we have remained cognizant of the timing of market changes and regulatory implementation, particularly as they affect observations made over the last few years, many fairly recent studies are already somewhat dated. Also, problems that might have been resolved or eased are not reported nearly as frequently as problems that have worsened.

- Similarly, participants in the town hall meeting on issues of IGIV access are most likely to be those who have experienced difficulties in their healthcare practices or with their own healthcare. The commentaries generated from the town hall meeting are not a statistically valid representation of the population of affected healthcare providers or patients.

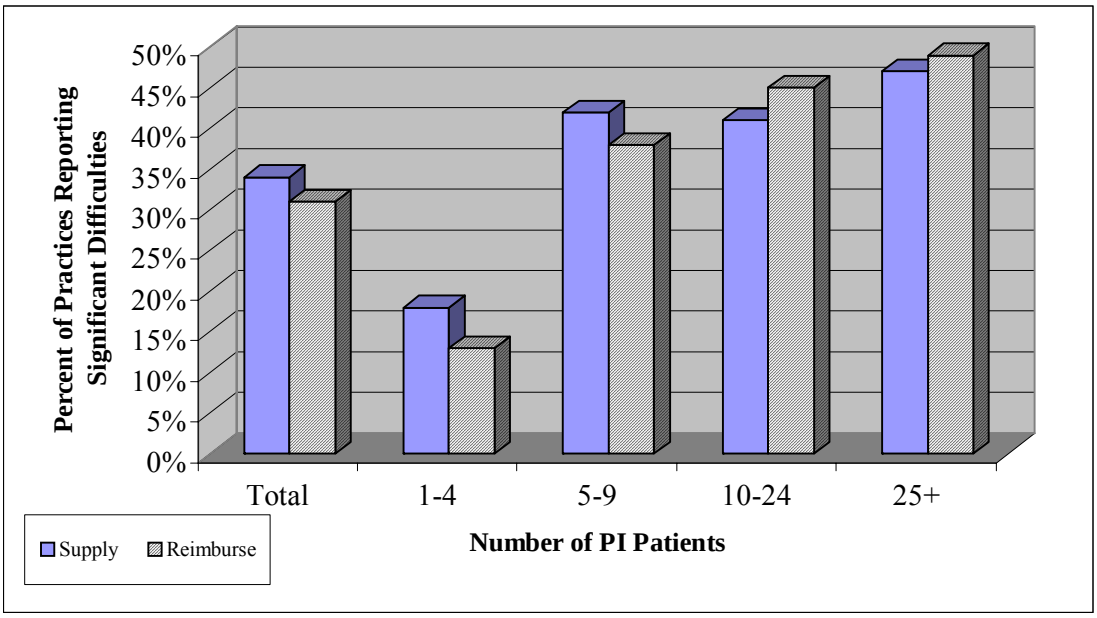
4.3. DIFFICULTIES PHYSICIANS, HOSPITALS, AND OTHER HEALTHCARE PROVIDERS HAVE HAD WITH ACCESS TO IGIV

4.3.1. Immune Deficiency Foundation (IDF) Surveys

IDF has undertaken several surveys of physicians treating PI patients (also see Section 3). These surveys included highly relevant questions to this research, including questions on supply/access (to IGIV) and Medicare and private insurance reimbursement issues. In the survey published in May 2005, conducted after Medicare physician reimbursement changes for Part B went into effect, approximately one-third of physicians treating PI patients reported significant difficulty in obtaining IGIV (IDF, 2005). Examples of such difficulties include having their IGIV brand changed, having treatments postponed, and other disruptions, as described further below.

The IDF 2005 physician survey results regarding supply and reimbursement impacts are illustrated in Figure 4-1, with the data categorized by the size of the practice in terms of number of PI patients. The results, based on an overall sample size of 248 physicians with PI patients that use IGIV, indicate that difficulties obtaining IGIV are fairly widely distributed across most size groups. It might appear likely that very small practices would have less favorable contracts for IGIV supplies, or relatively little capability to obtain products, but no such pattern appeared in these data.

Figure 4-1: Physician Reports of Significant Difficulties Obtaining IGIV Products, 2005



Source: IDF, 2005

In addition to its physician surveys, IDF has surveyed patients (IDF, 2006b) about IGIV access. These data provide a more recent look at access issues. IDF has followed a group of Medicare patients for several years and reports periodically on their status. Consistent with previous surveys, IDF found that approximately 70 percent of PI patients are receiving IGIV. Of the 1,009 responses received, IDF found 646 patients currently being treated with IGIV, 255 of whom were Medicare patients. Another 154 had stopped being treated with IGIV since January 2005, including 49 Medicare and 105 private insurance patients. Among these, Medicare patients were far more likely to say that they had discontinued IGIV

because the product was unavailable (16 percent to 5 percent) or due to lack of insurance (20 percent to 5 percent).

Tables 4-1, 4-2, 4-3, and 4-4 show the results for the most recent IDF patient survey. From their sample of 255 Medicare patients with PI, 32 percent had to change locations for their IGIV therapy since December 2004. Among non-Medicare patients, 19 percent changed locations for their IGIV therapy.

From Table 4-2, the most significant movement is the displacement of patients from physician's offices. A large number of these patients appear to have moved to home infusions, as is especially true for non-Medicare patients. Most private insurers reimburse home health care providers for the IGIV purchases based on AWP methodology.

Table 4-1: IDF Survey Question: Is the patient now getting IGIV treatments at the same location as in December 2004 (or at the same location they were given most recently before that time)?

Patient Category	Same Location	Not at Same Location	Number of Patients Surveyed
Medicare	68%	32%	255
Non-Medicare	81%	19%	391

Source: IDF, 2006b

Table 4-2: IDF Survey Question: Immediately prior to 2005, where were the IGIV treatments usually given? Where is the patient getting treatments now?

Location	Medicare Patients		Non-Medicare Patients	
	2004	2006	2004	2006
At home	23%	25%	50%	55%
Doctor's office [a]	22%	9%	13%	14%
Hospital inpatient	5%	5%	2%	1%
Outpatient	23%	28%	15%	11%
Hospital clinic [a]	27%	32%	21%	21%
Infusion suite	8%	7%	6%	6%
Other	0%	2%	2%	2%

Source: IDF, 2006b
[a] Difference between Medicare and non-Medicare patients significant at the 5 percent level.

Table 4-3: IDF Survey Question: What was your understanding of the reason for the change [of treatment location]?

Reason	Medicare	Non-Medicare
Location closed	3%	5%
Convenience	9%	27%
Unhappy with service	7%	9%
Doctors recommendation	12%	15%
Reimbursement [a]	54%	11%
IGIV unavailable [a]	27%	14%
Moved	7%	15%
Other	29%	37%
Number of respondents	90	88

Source: IDF, 2006b
[a] Difference between Medicare and non-Medicare patients significant at the 5 percent level.

IDF also collected comments on the types of problems PI patients have encountered. For example, Medicare patients were more likely (27 percent; not shown in table) to report more problems getting their IGIV treatments than non-Medicare patients (12 percent). Table 4-4 shows the types of

difficulties patients have been encountering. Both Medicare and non-Medicare patients were fairly likely (32 percent and 31 percent) to have had to switch to another brand of IGIV since the beginning of 2005. Medicare patients were more likely than non-Medicare patients (24 percent to 14 percent) to report that their treatment had to be postponed at some juncture since January 2005. Medicare patients were also much more likely (7 percent to 1 percent) to report that their dosage had been reduced since January 2005.

Table 4-4: IDF Survey Question: Which of the following problems, if any, has the patient experienced since the beginning of 2005? (Percentage of Patients)

Treatment Problem	Medicare	Non-Medicare
Treatment(s) postponed [a]	41%	28%
Had to switch brands	49%	51%
Treatment intervals increased [a]	18%	12%
Dose decreased [a]	13%	5%
Had to pay more	16%	20%
Other	15%	10%
None of these	36%	40%

Source: IDF, 2006b
[a] Difference between Medicare and non-Medicare patients significant at the 5 percent level.

4.3.2. American Society of Clinical Oncologists (ASCO) Survey

ASCO surveyed its oncology centers to determine the extent of access problems among its membership. Table 4-5 presents the principal findings from the ASCO survey. A total of 81 offices responded. Of the respondents, 41 percent had not been able to purchase as much of the product they sought. Respondents reported that on average they have purchased 67 percent of what they sought. Slightly over half of the respondents have not been able to get the IGIV products that they wish to prescribe. Also, 42 percent of physicians reported that they found it necessary to provide less than a full dose to some patients. As shown in the table, a variety of other measures are also employed to stretch the IGIV supplies obtained.

Table 4-5: ASCO Survey of Clinical Oncologists

ASCO Survey Question	All Survey Respondents			Small Practice Respondents [a]		
	Count	Percent	Mean	Count	Percent	Mean
1. Have you administered IGIV to patients in your practice at any time over the last 6 months?						
Yes	70	86.0%		53	98.1%	
No	11	14.0%		1	1.9%	
Total respondents	81			54		
2. Have you experienced any of the following problems obtaining IGIV over the past 6 months? Please check all that apply.	70	100%		53	100%	
Not able to obtain the full quantity of IGIV needed for patients for whom IGIV therapy has been prescribed	29	41.4%		19	35.8%	
Indicate the percentage, on average, of the total quantity ordered that your practice is actually able to obtain.	24		67%	16		62%
Not able to get the same IGIV product consistently	36	51.4%		27	50.9%	

ASCO Survey Question	All Survey Respondents			Small Practice Respondents [a]		
	Count	Percent	Mean	Count	Percent	Mean
Experienced significant delays in obtaining IGIV	36	51.4%		26	49.1%	
Other	28	40.0%		22	41.5%	
3. If you have experienced problems obtaining IGIV, how has this affected treatment in your practice of patients for whom IGIV therapy has been prescribed? Please check all that apply.	64			49		
Altered treatment plans to decrease the number of patients who are prescribed IGIV therapy	23	35.9%		16	32.7%	
Given patients a mixture of more than one IGIV product at a time in order to give them a full dose	12	18.8%		9	18.4%	
Given patients who are receiving IGIV therapy fewer treatments	20	31.3%		15	30.6%	
Given patients less than a full dose of IGIV	27	42.2%		23	46.9%	
No longer give IGIV to patients in our practice	10	15.6%		10	20.4%	
Refer patients to other practices in the area for IGIV	4	6.3%		3	6.1%	
Refer patients to the local hospital for IGIV	34	53.1%		25	51.0%	
Other	17	26.6%		11	22.4%	
4. If you have experienced problems obtaining IGIV, how do these problems compare for the lyophilized versus non-lyophilized drugs? Please check one of the following.	54			40		
Equally difficult to obtain lyophilized and non-lyophilized IGIV	40	74.1%		30	75.0%	
More difficult to obtain lyophilized IGIV than non-lyophilized IGIV	10	18.5%		7	17.5%	
More difficult to obtain non-lyophilized IGIV than lyophilized IGIV	4	7.4%		3	7.5%	
9. Please estimate the percentage of patients in your practice for whom IGIV is prescribed that have Medicare as a primary insurer.	53		56.2%	44		56.2%
10. From which of the following entities does your practice acquire/purchase IGIV products? Please check all that apply.						
Pharmaceutical distributors	41	65.1%		31	62.0%	
Group purchasing organizations	30	47.6%		21	42.0%	
Specialty pharmacies	18	28.6%		16	32.0%	
Pharmacies	0	0.0%		0	0.0%	
Manufacturers	11	17.5%		6	12.0%	
Local hospitals	2	3.2%		1	2.0%	
Other practices	2	3.2%		2	4.0%	
Other	7	11.1%		4	8.0%	

Source: Bailes, 2006
[a] Ten or fewer oncologists

The ASCO survey provides a limited glimpse of conditions for one group of affected practitioners. As noted previously, the survey was informally conducted and data are not adequate to judge the representativeness of the results. Nevertheless, because some oncologists are fairly intensive

users of IGIV therapy, the survey indicates that IGIV supplies are problematic for at least this select and affected group.

4.3.3. Hospital Difficulties with Access to IGIV

This section summarizes data from several sources on IGIV access for hospitals, including a survey of public hospitals, additional information collected by IDF, and information we gathered about hospital circumstances. Before reviewing the survey data, it is worthwhile to consider how hospitals typically respond to potential product availability problems.

4.3.3.1. Hospital Guidelines or Protocols on IGIV Use

Some hospitals have responded to tight IGIV supplies by instituting internal protocols or guidelines to govern the prescribing of IGIV. Other hospitals have not found it necessary to employ protocols in the current market.

Hospital experience with IGIV prescribing protocols extends back at least to an IGIV supply shortage of the late 1990s. IGIV supplies at that time were limited. In a testimony before the FDA Blood Products Advisory Committee in June of 1999, Patrick Schmidt, CEO and president of FFF Enterprises, declared that "nearly every institution in the country has implemented IGIV utilization guidelines" (Schmidt, 1999). Boulis et al. (2002) noted that the guidelines employed at the time varied in structure from formal schematics to informal agreements. In the current market, some hospitals have renewed their use of existing protocols.

The PHPC survey also asked its members about IGIV usage protocols. According to their 2006 survey, 56 percent of their hospitals have implemented (to varying degrees) protocols for prescribing IGIV drugs in response to a restricted supply (PHPC, 2006).

The effect of hospital protocols on total demand for IGIV will vary with the supply situation of the hospital. The protocols are a method for monitoring and controlling demand, but they generally provide the flexibility to adjust use to reflect available supplies of a product. A fundamental concept in writing protocols for hospitals dispensing IGIV is the categorical usage priority based on 1) weight of clinical evidence, 2) alternative treatment availability/effectiveness, and 3) the severity of the patient's condition (CBS, 2002). As is expected, lowest priority is given to those conditions for which the effectiveness of IGIV has not been proven. In such cases, prescription of IGIV is disallowed or administration is only allowed with special prior authorization. Protocols using categorizations of indications appear to be similar across the board, although the guidelines may vary slightly in the number of categories defined.

An example of an early protocol, developed in 1997 at Texas Children's Hospital (TCH), has been described in the literature. To implement the guidelines the Task Force initiated the use of an IGIV order form. Under the 1997 TCH guidelines:

"IGIV would be dispensed *only* to patients with the following conditions:
- Primary immunodeficiency disorders (e.g., severe combined immune deficiency, agammaglobulinemia, common variable immune deficiency, ataxia telangiectasia, etc)
- Kawasaki disease
- Idiopathic thrombocytopenic purpura with hemorrhage
- Guillain-Barre´ syndrome with ascending paralysis
- Post-bone marrow transplant *and* one of the following:

1. Cytomegalovirus (CMV) pneumonia or pneumonia consistent with a viral process (including CMV);
2. Documented viral infection involving the central nervous system, gastrointestinal system or liver;
3. CMV antigenemia." (Gurwitch et al., 1998)

Any patients not meeting these criteria were subject to a review by the Pharmacy and Therapeutics Committee Chairperson.

According to a study of the IGIV guideline implemented at Texas Children's Hospital, the facility reduced its usage of IGIV by 90 percent (Gurwitch et al., 1998). This result appears to be extreme relative to current hospital practices. We do not have information, however, on the extent to which use of existing hospital protocols or guidelines might reduce demand below levels that would otherwise exist.

Foreign nations have responded to IGIV market difficulties in similar ways. In 2000, a Canadian conference sponsored by Canadian Blood Services was organized to promote priority-setting and the optimization of IGIV usage across Canada. As part of the conference, a consensus panel determined that procedures should exist to prioritize IGIV utilization. Specifically, the panel recommended prioritization based on "(1) strength of evidence, (2) severity of the condition, particularly life-threatening conditions (e.g., neonatal sepsis, autoimmune thrombocytopenia, immunodeficiency), and (3) availability of alternative treatments." In addition, they determined that the "use of IGIV should be cost effective, i.e., given alternate equally effective and toxic interventions, the least costly should be chosen" (CBS, 2002). The panel recommended the use of such prioritization at all times, not just in times of shortage.

Given the current conditions, hospitals have moved to renew their use of or create new internal protocols. For example, beginning in November 2005, Shands HealthCare at the University of Florida implemented a prior-approval-based process for IGIV usage. Two staff physicians provide oversight for the practice. In times of limited supply, approvals are given to "higher priority uses" based on patient need and alternative treatments are recommended when possible (Shands, 2005).

Table 4-6 shows an example of a current, active IGIV usage guideline developed by the University of Michigan Health System. This protocol prioritizes patients into three categories. Assuming that it is reasonably representative, this protocol suggests that some patients with serious conditions might be excluded from IGIV treatment. Myositis patients, for example, are grouped in Category 2 in this protocol.

4.3.3.2. Public Hospital Pharmacy Coalition (PHPC) Survey

The Public Hospital Pharmacy Coalition (PHPC) surveyed its membership in February 2006 about access to IGIV. This coalition represents the public hospitals that serve as provider of last resort for indigent populations, which are referred to as 340B hospitals. Because they serve indigent populations these hospitals qualify for special discount pricing of pharmaceuticals. One of the main topics of the PHPC survey is whether such discounted IGIV has been available.

Table 4-7 is a summary of PHPC's findings. As the PHPC data indicate, approximately half of the public hospitals report being able to obtain enough IGIV to fulfill patients' needs. The severity of the shortfall was not reported. The PHPC members also reported consistent difficulties obtaining IGIV at the 340B discount rate.

Table 4-6: IGIV Usage Guidelines of the University of Michigan Health System

Category I:
Those who have highest priority for IGIV and will receive it preferentially over others when IGIV supply is limited. No approval for use is required.

- Primary immunodeficiency syndromes
  - X-linked agammaglobulinemia (Bruton's)
  - Severe combined immunodeficiency syndrome (SCID)
  - Other (use needs to be described when ordering IGIV)
- Kawasaki disease
- Neurological disorders
  - Guillain-Barré Syndrome (acute)
  - Chronic inflammatory demyelinating polyneuropathy (CIDP)
  - Multifocal motor neuropathy (MMN)
- Transplantation
  - Prolonged, severe hypogammaglobulinemia (IgG < 400 mg/dL) in allogenic HSCT recipients Check IgG levels monthly and adjust dose to maintain trough serum IgG concentrations > 400–500 mg/dL (most recent IgG levels need to be noted by prescriber when ordering IGIV)
  - Positive cross-match and/or HLA-incompatibility prior to and in renal transplantation
  - Humoral rejection in renal transplantation
- Pediatric patients with IgG deficiency or HIV and hypogammaglobulinemia, and who experience recurrent serious bacterial infections
- Neonatal alloimmune thrombocytopenia (NAIT)

Category II:
Those for whom therapy with IGIV will be considered on case-by-case basis when IGIV supply is limited. Approval for use is required when IGIV supply is limited. Pharmacy will announce when supply is limited.

- Common variable immune deficiency (CVID)
- Myasthenia gravis
- Immune thrombocytopenia purpura (ITP)
- Highly sensitized anti-HLA antibodies (PRA > 30%) prior to cardiac transplantation
- Severe parvovirus B19 infection (presenting with red cell aplasia, glomerulopathy, severe vasculitis, etc.)
- Polymyositis, dermatomyositis, systemic vasculitis (severe disease not responsive to other therapies)

Category III:
Indications for which IGIV should NOT be routinely used. Approval for use is required.

- Selective IgA deficiency not accompanied by defects in IgG production
- Infection prophylaxis in HSCT recipients with IgG > 400 mg/dL, and who are > 90 days post-HSCT, or routine GVHD prophylaxis
- Infection prophylaxis in low-birthweight neonates
- CMV prophylaxis
- Rotavirus infection
- Parainfluenza infection
- Sepsis and septic shock
- Autoimmune hemolytic anemia
- Systemic lupus erythematosus
- Monoclonal gammopathy of undetermined significance
- Pediatric intractable epilepsy
- Steroid-dependent asthma
- Antiphospholipid syndrome

Source: University of Michigan Health System, 2006

Table 4-7: Summary of Survey Results for Public Hospital Pharmacy Coalition on IGIV Access, 2006

Survey Question	Number of Responses	Yes	No	% Yes	% No
Able to obtain IGIV from wholesaler or distributor?	107	73	34	68.2%	31.8%
Able to obtain some amount of IGIV at 340B price?	98	21	77	21.4%	78.5%
Able to obtain enough IGIV to fulfill hospital's patients needs?	75	38	37	50.7%	49.3%
Able to obtain a written explanation as to why IGIV is unavailable at 340B price from manufacturer?	64	0	64	0.0%	100.0%
Able to obtain a written explanation as to why IGIV is unavailable at 340B price from distributor?	69	0	69	0.0%	100.0%

Source: PHPC, 2006

4.3.3.3 IDF Survey of Hospital Pharmacy Directors

The IDF hospital survey also covered protocols for use and treatment prioritization by hospitals. In its survey of 310 hospital pharmacy directors, 37 percent of hospitals had in place a Patient and Treatment Committee for determining which patients would receive IGIV and 27 percent had a priority protocol which defined which patients would be infused. Table 4-8 gives the full IDF findings on these points.[16]

The IDF survey gives some idea of the top priorities for IGIV therapy. As also noted in Table 4-8, 29 percent of these hospitals report that all on-label uses are given priority. Otherwise, the only individual condition given priority by a majority of hospitals is primary immune deficiency. Other individual on-label uses, such as Kawasaki disease, are given priority in only a minority of cases.

4.3.3.4. Investigation of Instances of Hospitals Denying IGIV Therapy to Patients

At the September 2006 public meeting, comments were made about the lack of IGIV access in some regions. This section describes our efforts to confirm the range of difficulties in access.

In various comments at the meeting, Florida was described as a state where access problems were particularly acute, with only a few hospitals providing IGIV on an outpatient basis. A representative of the Florida Hospital Association (FHA) stated that they had surveyed Florida hospitals earlier in 2006 and determined that only a few were accepting new outpatients with diseases requiring IGIV therapy. According to FHA, the hospitals attributed the problem to their inability to acquire sufficient IGIV, not to reimbursement problems. The FHA spokesperson reported that both Medicare and non-Medicare patients appeared to be affected. The spokesperson also reported that the problem did not appear to have improved since early in 2006 (Reep, 2006).

IDF and other commenters at the public meeting identified hospitals in several other states that have discontinued or limited access to IGIV therapy for outpatient services. These comments covered selected hospitals in Wisconsin, Texas, Missouri, Nebraska, Alabama, and New York. IDF has assembled various emails and letters from healthcare institutions in these states describing a variety of difficulties, such as shortfalls of manufacturer shipments and inadequate allocations.

[16] The IDF survey results do not make clear whether those hospitals with a use committee but without a priority protocol behaved in a different fashion than those hospitals with a priority committee.

Table 4-8: IDF Survey Results on Existence of Hospital Protocols for IGIV Use (Sample Size = 62)

Survey Question	Response
Does your hospital have a Patient and Treatment Committee that determines which patients will be treated with IGIV?	
Yes	37%
No	60%
Don't Know	3%
Does your hospital have a priority protocol specifying which patients will be infused?	
Yes	27%
No	70%
Don't Know	3%
Which conditions have priority:	
Primary Immune Deficiency?	56%
Immune Thrombocytopenic purpura?	26%
Chronic lymphocytic leukemia?	19%
Kawasaki Disease?	13%
Bone Marrow Transplantation?	10%
Pediatric HIV infection?	2%
All on-label uses?	29%
Other?	3%
Don't know?	11%

Source: IDF, 2007a

We contacted pharmacy personnel in a number of hospitals named directly or indirectly in the public meeting. (The individual hospitals have not been named here.) In three cases, the commentary suggested problems obtaining IGIV therapy in a local geographic area but did not identify individual hospitals where service was being denied. In all, we contacted eight hospitals and asked them whether they had discontinued IGIV therapies. The survey was intended to confirm the existence of adverse healthcare conditions for IGIV patients. It was not random; its results cannot be extrapolated over any geographic area and are only intended as a glimpse of availability in certain regions with rumored IGIV access problems.

We confirmed that one hospital had discontinued IGIV therapy for outpatients in July 2006. Two other hospitals were not providing IGIV therapy to outpatients but had never provided it. The five remaining hospitals indicated that they provided IGIV therapy, although one had some restrictions on the range of conditions it was treating. Overall, the three hospitals not offering IGIV therapy are for-profit hospitals and those offering IGIV therapy are not-for-profit hospitals.

In the course of our broader interviewing for this study, we interviewed several hospital pharmacies regarding their ability to obtain IGIV and the adequacy of reimbursement. Several hospitals reported receiving monthly allocations that were barely adequate to cover patient demand. Several reported, however, some month-to-month uncertainty about the adequacy of their supply. These hospitals sometimes had to buy additional product from the secondary market, often at prices well above their normal contract rates. One hospital had ceased IGIV therapy on an outpatient basis. This hospital continued to receive its current IGIV allocation. When that allocation was more than they needed for limited internal uses, they transferred it to other hospitals in their network. Other hospitals reported having extra IGIV in some months, which they then stored in anticipation of future problems.

We also received information in the course of other interviews that hospitals in Texas had sharply restricted IGIV therapy to new outpatients. Specifically, two neurologists reported that hospitals in that area had restricted access to IGIV therapy. One hospital has instituted a Committee on Use of IGIV in September 2006 that required a member of the committee approve each IGIV prescription. The

committee enforces a hospital protocol that generally does not allow off-label uses of the product, with the possible exception of severely ill patients. One neurologist reported that had been forced by the hospital protocol to treat a number of his neurology Medicare patients with alternative therapies. This had been successful in some cases and not successful in others. For the latter cases, additional alternative therapies were not being tried.

One hospital offered a breakdown of their supply request for 2005, as shown below in Table 4-9. The hospital received less than requested amounts of two products and more than requested of a third. On balance, however, the hospital received approximately 20 percent less than it requested.

Table 4-9: One Hospital's Supply Request and Allocation for IGIV in 2005

Drug	Quantity Requested	Quantity Received	Product Shortfall or Surplus	Cumulative Shortfall or Surplus
Panglobulin NF	700	500	-200	-200
Polygam SD	810	600	-210	-410
Bayer Gamunex	60	100-200 (150 used)	90	-320
ZLB Behring Carimune	40	40	0	-320
All other IGIV	0	0	0	-320
Total	**1,610**	**1,290**	**NA**	**-320**
Percentage shortfall	**NA**	**NA**	**NA**	**19.9%**

Despite the indications of some denials of IGIV therapies in hospital settings, CMS data on Medicare beneficiaries by site of service do not indicate a reduction in the total number of unique Medicare beneficiaries receiving IGIV. While we present these data in full further below, the data indicate a transfer of approximately 2,700 patients from physician's offices to hospitals between the 4th quarter of 2004 (prior to the change in reimbursement) to the 1st quarter of 2006.

The CMS data might mask some of the individual difficulties for Medicare patients in obtaining IGIV (see Table 4-20). Patients who have had their therapies reduced or who missed infusions would still be counted in the unique beneficiaries totals if they received any infusions during the quarter. IDF's hospital pharmacy survey found that 32 percent of hospitals had to turn away one or more patients during 2006.

The IDF survey authors also provided a geographic breakdown of the hospitals that had turned patients away, and the reasons for their actions. The regional breakdown of responses to these questions, are presented in Table 4-10. The data show that number of denials of IGIV therapy were highest in the South Atlantic states (23), but that significant number of hospitals had to deny IGIV therapy in many regions (e.g., 8 to 14 hospitals). The data show that the predominant reason that patients were turned away was inadequate product supplies. A small share of hospitals gave reimbursement as the reason for the denials of therapy. As of this publication, we lack CMS data on the number of Medicare beneficiaries receiving IGIV in hospitals for the last three quarters of 2006. The table also shows the average prices paid for IGIV in each region. The highest prices among the surveyed hospitals for liquid IGIV are paid in the Mid-Atlantic states. The South Atlantic states, where denials of service were relatively high, paid the median price for liquid IGIV but the third highest price for lyophilized IGIV. Nevertheless, as noted by the hospitals, availability rather than reimbursement is the principal cause of the denials of service.

The IDF survey of hospital pharmacy directors found that 3.2 percent of hospitals "probably will not" continue to treat patients under current IGIV reimbursement practices and that 36.6 percent are uncertain or do not know whether they would continue to treat IGIV patients (see Table 4-11). The last statistic is difficult to interpret because it could represent either genuine uncertainty about the

Table 4-10: IDF Survey of Hospital Pharmacy Directors: What is the average price you pay for one gram of IVIG? And has your hospital had to turn away patients needing IVIG treatment?

Question/Response Choice [a]	New England	Mid-Atlantic	East North Central	West North Central	South Atlantic	East South Central	West South Central	Mountain	Pacific	Total
What is the average price you pay for one gram of liquid IVIG? (Sample size = 158)										
Count	12	20	21	16	27	16	26	11	9	158
Mean	$58.83	$75.10	$54.52	$57.88	$62.89	$63.75	$67.58	$46.73	$65.11	$62.37
Standard Deviation	$10.41	$54.75	$8.20	$18.99	$29.16	$33.03	$30.14	$15.46	$15.47	$29.74
What is the average price you pay for one gram of lyophilized IVIG? (Sample size = 126)										
Count	7	21	21	14	23	12	13	7	8	126
Mean	$47.71	$56.29	$49.00	$54.50	$58.30	$65.25	$64.15	$40.43	$56.75	$55.58
Standard Deviation	$4.65	$25.50	$13.16	$20.72	$26.42	$28.19	$24.90	$17.32	$23.08	$22.71
Since the beginning of 2006, has your hospital had to turn away patients needing IVIG treatment? (Sample size = 309)										
Yes	2 12.5%	14 28.0%	14 27.5%	5 18.5%	23 40.4%	7 30.4%	14 33.3%	8 44.4%	11 44.0%	98 31.7%
No	12 75.0%	31 62.0%	37 72.5%	20 74.1%	33 57.9%	16 69.6%	27 64.3%	10 55.6%	14 56.0%	200 64.7%
Don't know	2 12.5%	5 10.0%	0 0.0%	2 7.4%	1 1.8%	0 0.0%	1 2.4%	0 0.0%	0 0.0%	11 3.6%
Total	16 100.0%	50 100.0%	51 100.0%	27 100.0%	57 100.0%	23 100.0%	42 100.0%	18 100.0%	25 100.0%	309 100.0%
Did you turn away patients because of… (Sample size = 98)										
Staffing or capacity shortage?	1 50.0%	5 35.7%	2 14.3%	0 0.0%	6 26.1%	2 28.6%	5 35.7%	1 12.5%	1 9.1%	23 23.5%
Product availability?	2 100.0%	14 100.0%	13 92.9%	5 100.0%	20 87.0%	7 100.0%	13 92.9%	8 100.0%	10 90.9%	92 93.9%
Inadequate insurance (reimbursement)?	0 0.0%	1 7.1%	1 7.1%	1 20.0%	2 8.7%	0 0.0%	2 14.3%	0 0.0%	0 0.0%	7 7.1%
Other reasons?	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	1 7.1%	0 0.0%	0 0.0%	1 1.0%
Total	2 100.0%	14 100.0%	14 100.0%	5 100.0%	23 100.0%	7 100.0%	14 100.0%	8 100.0%	11 100.0%	98 100.0%

Source: IDF, 2007c

[a] The sample size excludes those who refused to answer the question.

Table 4-11: IDF Hospital Pharmacy Directors Survey: Will your hospital continue to treat patients under current reimbursement practices?

Question/Response Choice [a]	New England	Mid-Atlantic	East North Central	West North Central	South Atlantic	East South Central	West South Central	Mountain	Pacific	Total
Ability of your hospital to continue to treat patients under current IVIG reimbursement practices (Sample size = 309)										
Definitely will	4 25.0%	8 16.0%	15 29.4%	6 22.2%	13 22.8%	4 17.4%	10 23.8%	7 38.9%	7 28.0%	74 23.9%
Probably will	6 37.5%	22 44.0%	13 25.5%	12 44.4%	20 35.1%	9 39.1%	9 21.4%	6 33.3%	13 52.0%	110 35.6%
Probably will not	0 0.0%	1 2.0%	0 0.0%	0 0.0%	3 5.3%	1 4.3%	3 7.1%	1 5.6%	1 4.0%	10 3.2%
Definitely will not	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%	2 4.8%	0 0.0%	0 0.0%	2 0.6%
Uncertain/Don’t know	6 37.5%	19 38.0%	23 45.1%	9 33.3%	21 36.8%	9 39.1%	18 42.9%	4 22.2%	4 16.0%	113 36.6%
Total	16 100.0%	50 100.0%	51 100.0%	27 100.0%	57 100.0%	23 100.0%	42 100.0%	18 100.0%	25 100.0%	309 100.0%

Source: IDF, 2007c

[a] The sample size excludes those who refused to answer the question.

sustainability of current practices or an ignorance about or unwillingness to speculate about future hospital policy changes.

We acknowledge that there have been difficulties in the provision of IGIV therapy to patients by hospitals in certain areas of the United States. Our data, however, are far too limited to characterize the nature and extent of these problems reliably. The CMS data are fairly definitive in showing that the overall number of Medicare beneficiaries receiving IGIV at hospitals actually increased through the first quarter of 2006. These data could mask occasional interruptions in service for some patients, however.

4.4. DIFFICULTIES PHYSICIANS, HOSPITALS, AND OTHER HEALTHCARE PROVIDERS HAVE HAD WITH REIMBURSEMENT FOR IGIV

This section focuses on the adequacy of reimbursement under the Medicare program. The discussion considers the various parts of Medicare including Part A (Hospital Services), Part B (Medical Services), Part D (Prescription Drug Coverage), and the reimbursement provisions of the Medicare Prescription Drug Improvement and Modernization Act of 2003 (MMA), P.L. 108-173. Sections 4.4.1 and 4.4.2 describe the Medicare coverage provisions as they relate to IGIV therapies. Sections 4.4.3 and 4.4.4 examine how the change in reimbursement patterns created by MMA has affected healthcare providers and their ability or incentive to provide home healthcare services.

4.4.1. Medicare Coverage Provisions

Section 1886(d) of the Social Security Act established a prospective payment system to cover the operating costs of acute care hospital inpatient stays under Medicare Part A. Under the system, each case is categorized into a diagnosis-related group (DRG). Each DRG has a payment weight assigned to it, based on the average resources used to treat Medicare patients in that DRG. Under DRG, there would be no separate payment for IGIV given in inpatient settings (i.e., per diem payment is all inclusive of drugs, supplies, and labor). Under Part A, after a deductible is paid, most hospital visits are covered. Lengthy hospital stays, i.e., those longer than 60 days, require a co-pay for each additional day in the hospital.

Prior to 2005, CMS pricing for most Part B drugs was based on the average wholesale price (AWP). Congress determined that the AWP-based reimbursement resulted in excessive payments for drugs and endeavored to reform the reimbursement system. Before the MMA, IGIV was reimbursed at 95 percent of AWP.

In January 2005, Medicare, which is administered by CMS, began paying for most Part B drugs using a new pricing methodology based on average sales prices (ASP). For 2004, the reimbursement amount for IGIV was based on 80 percent of the AWP, as published in national pricing compendia such as the "Red Book®."[17] The MMA defines an ASP as a manufacturer's sales of a drug to all purchasers in the United States in a calendar quarter divided by the total number of units of the drug sold by the manufacturer in the same quarter. The ASP is the net of any price concessions such as volume discounts, prompt pay discounts, and cash discounts; charge-backs, other discounts, and rebates other than those obtained through the Medicaid drug rebate program.

[17] In 2004, most covered drugs were paid at 85 percent of AWP. The law, however, stipulated an alternate percentage in 2004 for certain high volume drugs that had been studied by the Office of Inspector General (OIG) and the General Accounting Office (GAO). IGIV was one of those drugs for which reimbursement was set at 80 percent of AWP. Prior to the MMA, the Medicare payment rate for IGIV was 95 percent of AWP.

Manufacturers report ASP by National Drug Code (NDC) numbers, which are 11-digit identifiers that indicate the manufacturer, the product dosage form, and the package size of a drug. CMS reimburses healthcare providers for drugs using procedure codes. Using the ASP pricing methodology, the Medicare allowance for most Part B drugs is equal to 106 percent of the ASP. Under Part B, patients pay a deductible and a co-pay of 20 percent for most physician and medical services.

The changeover to the new ASP methodology was staggered, with physician's offices and infusion suites switched in January 2005 and hospital reimbursement modified in January 2006. Additionally, the MMA also created the Medicare Part D retail drug benefit. Under Part D, patients are partially reimbursed for drug costs. The co-pay requirements under Part D for an individual who does not qualify for a low-income subsidy are as follow: Patients pay for the first $250 of drug costs, pay 25 percent of costs for the next $2,000, and then pay 100 percent of costs from $2,250 to $5,100. The co-pay for costs over $5,100 is 5 percent.

As of January 1, 2004, the MMA covered IGIV therapy for primary immunodeficiency diseases in the home. Medicare pays for the drug if medically appropriate, but not for supplies or services related to the administration of IGIV. Table 4-12 shows the reimbursement rates for the drug purchase in 2006 under Medicare Parts A, B, and D.

Table 4-12: Reimbursement Rates in 2006 Under Medicare Parts A, B and D

Site of Care	Medicare Section	Reimbursement Basis	Type of IGIV	1st Qtr	2nd Qtr	3rd Qtr
Hospital inpatient	Part A	Based on diagnosis-related groups	Liquid	Paid as part of diagnosis-related group reimbursement [a]		
			Lyophilized			
Hospital outpatient	Part B – HOPPS	ASP	Liquid	$56.72	$58.18	$60.65
Physician's office	Part B	ASP	Lyophilized	$44.44	$44.52	$50.53
Patient home	Part B – durable medical equipment	Not applicable	Not applicable to IGIV	Not covered	Not covered	Not covered
		AWP	Vivaglobin [b]	$120		
	Part B –Applicable only to PI patients	ASP	Liquid	$56.72	$58.18	$60.65
		ASP	Lyophilized	$44.44	$44.52	$50.53
	Part D	AWP	Liquid	$82.50 [c]		
		AWP	Lyophilized	$79.91 [c]		

Source: Based on Red Book, 2006 (simple average of AWPs per gram)
NA= Not available
[a] Hospital inpatient reimbursement is fixed and based on patient's diagnosis regardless of IGIV use.
[b] Vivaglobin is a subcutaneous product, which generally requires an infusion pump.
[c] Represents average AWP less 20 percent for the category. Actual reimbursement rates could vary depending upon the specific prescription drug plan.

4.4.2. Medicare Reimbursement Patterns for On- and Off-Label IGIV Infusions

To examine Medicare coverage of the various on- and off-label IGIV treatments, we examined the Medicare National Coverage Determinations (NCDs) and a selection of Medicare Local Coverage Determinations (LCDs). The NCDs and LCDs define the medical treatments that will be reimbursed by Medicare and are based on reviews of the standards for medical care and on evidence of the effectiveness of various medical treatments.

More precisely, an NCD is developed by CMS to define national coverage for a specific medical service, procedure or device. An LCD, as established by Section 522 of the Benefits Improvement and Protection Act, is a decision by a fiscal intermediary or carrier on whether to cover a particular service on a Medicare intermediary-wide or insurance carrier–wide basis in accordance with Section 1862(a)(1)(A) of the Social Security Act (i.e., a determination as to whether the service is reasonable and necessary). In the absence of national policy, Medicare contractors develop LCDs to specify the criteria for which medical treatments, such as IGIV infusions, will be covered based on the advice and input of medical and specialty societies and the review of current medical practice, clinical data, and research studies. Thus the LCDs act as a screen for which IGIV uses Medicare approves for payment. Excluded indications might also be reimbursable but further reviews are required.

Most coverage decisions are made at the local level, although some NCDs are developed. The single NCD for IGIV use – covering the treatment of autoimmune mucocutaneous blistering diseases – has been in effect since 2002 (CMS, 2002). We reviewed eight contractor LCDs covering a variety of states for the indications that Orange et al. (2006) identified as beneficial .[18] Table 4-13 provides the results of this effort.

Additional criteria must be met for Medicare to allow coverage for the IGIV treatments listed. The efficacy of various (on- and off-label) uses is reviewed in the Medicare program. For example, the Kansas LCD for PI patients requires that after 1 to 2 years and at similar intervals thereafter, an attempt must be made to wean or stop the IGIV infusion. It also specifies that there must be periodic monitoring to justify the continued infusion. Table 4-14 describes some of the additional requirements for other IGIV-treatable conditions. These include a demonstrated failure of other treatment strategies, evidence that the disease is rapidly progressing, or documentation that the patient has low IgG concentrations.

Table 4-13: Indications Approved Under a Sample of Local Coverage Determinations (LCDs)

Benefit	Disease	Percent of LCDs Covering IGIV Use Under Certain Conditions
Autoimmune Diseases		
Definitely beneficial	Primary immune deficiency	100
	Common variable immunodeficiency	
	Idiopathic thrombocytopenic purpura	
Probably beneficial	Dermatomyositis	100
	Polymyositis	88
Might provide benefit	Severe rheumatoid arthritis	13
	Autoimmune diabetes mellitus	0
	Vasculitides and antineutrophil antibody syndromes	0
	Autoimmune neutropenia	13
	Autoimmune hemolytic anemia	38
	Autoimmune hemophilia	0
	Systemic lupus erythematosus	0

[18] The Medicare Coverage Database is available at http://www.cms.hhs.gov/mcd/search.asp. IGIV LCDs reviewed include Empire Medicare Services, January 1, 2006 (covers New York); TriSpan Health Services, February 13, 2006 (covers Louisiana, Missouri, and Mississippi); Noridian Administrative Services, LLC, May 5, 2006 (covers primarily Alaska, Minnesota, North Dakota, and Washington); Blue Cross and Blue Shield of Montana, July 2, 2006 (covers Montana); Cahaba Government Benefit Administrators, LLC, August 15, 2006 (covers Alabama, Georgia, and Mississippi); Mutual of Omaha Insurance Company, August 31, 2006 (covers 47 states including California, Florida, and Texas); Highmark Medicare Services, September 9, 2006 (covers primarily D.C. and Maryland); and Blue Cross and Blue Shield of Arizona, September 15, 2006 (covers primarily Arizona).

Benefit	Disease	Percent of LCDs Covering IGIV Use Under Certain Conditions
Infectious and Infection-Related Diseases		
Definitely beneficial	Kawasaki disease	100
	Cytomegalovirus-induced pneumonitis in solid organ transplants	13–50 (dependent on organ)
	Rotaviral enterocolitis	0
	Bacterial infections in lymphoproliferative diseases and HIV	100
	Staphylococcal toxic shock	0
	Enteroviral meningoencephalitis	0
Neuroimmunologic Disorders		
Definitely beneficial	Guillain-Barré syndrome	100
	Chronic inflammatory demyelinating polyneuropathy	88
Probably beneficial	Lambert-Eaton myasthenic syndrome	75
	Stiff-man syndrome	13
	Myasthenia gravis	100
Might provide benefit	Monoclonal gammopathy multiple sclerosis	63
	Intractable childhood epilepsy	0
	Rasmussen syndrome	0
	Acute disseminated encephalomyelitis	0
	Cerebral infarctions with antiphospholipid antibodies	0
	Demyelinative brain stem encephalitis	0
	Lumbosacral or brachial plexitis	0
	Paraproteinemic neuropathy	13
	Postinfectious cerebellar ataxia	0
	Acute idiopathic dysautonomia	0
Miscellaneous Uses		
Probably beneficial	Toxic epidermal necrolysis and Stevens-Johnson syndrome	0
Might provide benefit	Severe, persistent, high-dose, steroid-dependent asthma	0
	Complications for bone marrow transplantation	100
	Complications in renal transplantation	50
	Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections	0
	Delayed-pressure urticaria	0
	Autoimmune blistering skin diseases and manifestation of systemic diseases (e.g., pemphigus)	100
	Chronic urticaria	0
	Acute myocarditis	0

Source: ERG analysis of the LCDs identified. The benefit and disease listing is based on Orange et al. (2006).
Note: The LCDs examined did not allow reimbursement for any of the diseases for which Orange et al. (2006) determined IGIV infusion was unlikely to be beneficial. These diseases have been removed from the disease listing. Additionally, any indications in Orange et al. (2006) that could not be clearly matched with the diagnosis codes in the LCDs have been removed. These indications include autoimmune liver disease; campylobacter species–induced enteritis; fetomaternal alloimmune thrombocytopenia; Graves ophthalmopathy; HTLV-1–associated myelopathy; IgM antimyelin-associated glycoprotein paraprotein–associated peripheral neuropathy; multifocal motor neuropathy; neonatal isoimmune hemolytic jaundice; neonatal sepsis; opsoclonus myoclonus; paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy; postoperative sepsis; posttransfusion purpura; pseudomembranous colitis; RSV lower respiratory tract infection.

Table 4-14: Additional Criteria for Indications Approved Under Two Local Coverage Determinations

Disease	Mutual of Omaha Insurance Co. (California, Florida, Texas)	Empire Medicare Services (NY)
	Additional Approval Criteria to Use IGIV	
Autoimmune Diseases		
Chronic idiopathic thrombocytopenic purpura	▪ Prior treatment with corticosteroids and splenectomy ▪ Duration of illness less than 6 months ▪ Age of 10 years or older ▪ No concurrent illness/disease explaining thrombocytopenia ▪ Platelet counts persistently at or below 20,000/mL	
Dermatomyositis and polymyositis	Requires individual consideration of situation for approval	▪ Unresponsive or intolerant to steroids and immunosuppressants or have serious side effects from steroids and/or immunosuppressives ▪ Measurable response within 6 months of use of IGIV
Infectious and Infection-Related Diseases		
Kawasaki disease	Within 10 days of onset of fever and when oral aspirin is used concurrently	No additional criteria
Cytomegalovirus-induced pneumonitis in solid organ transplants	Not specifically listed as covered/not covered	▪ Transplantation was for a Medicare covered indication ▪ Patient was seronegative for cytomegalovirus before transplantation, donor is seropositive
Bacterial infections in lymphoproliferative diseases and HIV	▪ Less than 13 years of age ▪ Entry CD4+ lymphocyte counts are greater than or equal to 200/mm^3	▪ Less than 13 years of age ▪ Entry CD4+ lymphocyte counts are greater than or equal to 200/mm^3 ▪ HIV is clinically symptomatic or asymptomatic, but immunologically abnormal
Miscellaneous Uses		
Complications for bone marrow transplantation	▪ Transplantation was for a Medicare covered indication ▪ 20 years of age or older ▪ Patient was seropositive for cytomegalovirus (CMV) before transplantation ▪ Patient was seronegative, had seronegative marrow donors, and was undergoing allogeneic transplantation for hematologic neoplasms	
Autoimmune blistering skin diseases and manifestation of systemic diseases (e.g., pemphigus) – NCD coverage	▪ Failed conventional therapy ▪ Conventional therapy is contraindicated ▪ Rapidly progressive disease (in these situations, IGIV therapy would be given along with conventional treatment(s) and the IGIV would be used only until conventional therapy could take effect) ▪ IGIV must be used only for short-term therapy and not as a maintenance therapy	
Guillain-Barré syndrome	▪ Paralysis at least sufficient to preclude walking 30 feet without assistance, and be in the first two weeks of their illness ▪ Documented improvement with IGIV and attempts to wean ▪ If improvement does not occur with IGIV, then infusion should not continue	▪ Other therapy has failed or is contraindicated, ▪ Difficulty with venous access for plasmapheresis, or ▪ Rapidly progressive forms of these diseases

Disease	Mutual of Omaha Insurance Co. (California, Florida, Texas)	Empire Medicare Services (NY)
	Additional Approval Criteria to Use IGIV	
Chronic inflammatory demyelinating polyneuropathy	▪ Unequivocal CIDP as defined by the mandatory clinical, physiologic, or pathologic criteria ▪ Proved refractory to, or intolerant of, prednisone or azathioprine given in therapeutic doses over at least three months or neuralgic function assessment score of at least three or greater on the Rankin Scale at the time of initial therapy, or documented improvement with IGIV and attempts to wean ▪ If improvement does not occur with IGIV, then infusion should not continue	
Myasthenia gravis	▪ Intolerant of, or refractory to, cholinesterase inhibitors, corticosteroids, and azathioprine ▪ Rapidly progressive and/or potentially life-threatening muscular weakness ▪ Documented improvement with IGIV and attempts to wean ▪ If improvement does not occur with IGIV, then infusion should not continue	
Lambert-Eaton myasthenic syndrome	Requires individual consideration of situation for approval	Not specifically listed as covered/not covered
Monoclonal gammopathy multiple sclerosis	Not covered	

Source: ERG analysis of the LCDs identified for approved conditions with 50 percent or greater coverage in Table 4-10

4.4.3. Home Infusion Reimbursement Rules Under Medicare

Table 4-15 presents a summary of reimbursement rules for all types of home infusion therapy, including IGIV. The rules for Medicare coverage are complex, with different reimbursement formats under different parts of Medicare.

Under Medicare Part A, patients can receive IGIV in the home if they are homebound, a circumstance that applies to a small share of patients. Relatively few companies that offer Medicare-certified nursing services also offer home infusion services. The drug, however, is excluded from the home healthcare benefit under Part A. It must be billed under Part B by a Medicare-certified nursing agency.

Part B includes a specific provision to allow reimbursement of the drug cost for home infusions of PI patients. There is no such inclusion for other patients with IGIV-treatable conditions. This Part B provision does not cover the costs of the infusion nursing services, only of the IGIV. Otherwise, under Part B, patients are covered for selected other specific home infusion therapies and/or medical conditions, although none of these other therapies or conditions include IGIV or IGIV-treatable conditions. For these therapies, CMS determined that the infusions always require the use of an electromechanical infusion pump. Vivaglobin, the only subcutaneous product falls under the DME coverage. (Otherwise, IGIV therapy might or might not use an infusion pump.)

Table 4-15: Reimbursement for Home Infusion Therapy for Medicare Beneficiaries

	Part A Home Health	Part B Benefit	Part C Medicare Advantage	Part D Prescription Drug Plan	State Medicaid Program	Other Payer Coverage
Requirement	Homebound and in need of part-time or intermittent skilled nursing or therapy services, if such services are reasonable and necessary to the treatment of the illness or injury	DME benefit – if medically necessary for the drug to be administered through an infusion pump [this applies to only 22 specific therapies and 32 medical conditions]; the subcutaneous IGIV product is covered Benefit for IGIV patients – patients with PI are covered Non-PI diagnoses are not covered	Coverage of at least Part A/B services; coordinated care plans may include additional coverage and mechanisms to control utilization	Drugs that are not currently covered under Parts A and B of Medicare, or otherwise excluded under Part D	Provided that coverage is not available through Parts A, B, C, or D of Medicare, Medicaid home health benefit may cover services, equipment and supplies necessary to administer home infusion drugs	Varies, but generally like Part C
Professional Fees	Yes	No	Yes	No	Yes – may be billed separately or as part of bundled rate	Varies, but generally like Part C
Equipment and Supplies	Sometimes – home health therapy responsible for providing hydration fluid and IV supplies if infusion is provided via gravity feed method	Yes – supplies are billed separately by a DME vendor to appropriate DME regional carrier Supplies are not covered under the benefit for PID patients	Yes – included in per diem payment (generally bundled)	No – cost of supplies, equipment, and professional fees must be covered via Medicare Parts A or B, Medicare Advantage Plan, Medicaid, other insurance, or out-of-pocket	Yes – may be billed separately or as part of bundled rate	Varies, but generally like Part C
Drug Ingredient and Dispensing Fee	No – drugs and biologicals are specifically excluded from the Part A home health benefit	Part B pays the drug costs as a part of the DME or PI benefit but no separate dispensing fee is paid	If covered under Part B, yes; if not covered under Part B, must be covered under Part D in a MA-PD plan	Yes	No – unless drugs are included in bundled rate, which does not trigger Medicaid FFP exclusion	Varies, but generally like Part C

Source: CMS, 2006, with additional modifications by ERG

Under Part C, patients can obtain additional coverage, such as HMO-type coverage, in Medicare Advantage programs. Patients who qualify for Part A (i.e., are over 65 and meet other conditions) and are enrolled in Part B can also select Part C coverage. IGIV coverage is defined by either Part B or Part D provisions.

Patients (other than those with PI) can obtain IGIV under their Part D plans if their infusions are not covered under either Parts A or B. The home infusion companies are reimbursed according to the terms of their contracts with prescription drug plans (PDPs). As of late 2006, many of these contracts reimburse home infusion companies at roughly AWP minus 15 percent. This level of reimbursement is generally sufficient for home infusion companies to provide home infusion therapies profitably. (Some specialty pharmacies have expressed concern, however, about whether this level of reimbursement will remain in effect for much longer, a topic that is discussed further below.)

Some dual-eligible patients receive IGIV in the home under combined Medicare and Medicaid coverage provisions. Reimbursement under Medicaid coverage is based on the AWP model and is generally considered adequate. Hospital discharge nurses, however, have reported considerable problems in placing dual-eligible patients with home infusion companies. This topic is discussed further below.

In summary, home infusion coverage rules are quite complex. Other than for the relatively few patients who qualify for Medicare-certified nursing services under Part A, the home infusion nursing service is not explicitly covered. With home infusions requiring 3 to 5 hours on site plus travel time, and pharmacy time to acquire and prepare the IGIV solution, the labor component of the service is significant. Patients with Medicare Part D are receiving home infusions because some home infusion company contracts with PDPs provide reimbursement based on AWP and it is sufficiently high to cover infusion company costs and profits.

4.4.4. Review of Reimbursement Level Sufficiency

One goal of the MMA was to separate reimbursement for the drug from reimbursement for the service. CMS clearly endeavored to separate the drug and the service reimbursement. Before the MMA, CMS's AWP-based reimbursement was overcompensating for the drug costs and subsidizing the other components of the infusion service. In the shift to ASP-based reimbursement, reimbursement for the drug cost has fallen. This change has affected healthcare providers in a variety of ways.

It is shown below that the phasing in of the new Medicare ASP plus 6 percent reimbursement level in 2005 created a shift of Medicare patients away from physician's offices and infusion suites. In 2006, with the phase-in of the ASP plus 6 percent reimbursement to hospital outpatient clinics, some hospitals have been unwilling to accept Medicare patients for IGIV infusion. Although not all instances are well documented, some Medicare patients sometimes found themselves having difficulty finding infusion sites.

In the public meeting, many commenters described the inadequacy of reimbursement. A large proportion of the healthcare providers who spoke at the public meeting criticized current reimbursement levels as inadequate for sustaining the treatment of patients needing IGIV infusions. For example, physicians commented that they had had to seek alternative treatment sites for their Medicare patients when the new Medicare reimbursement rates were instituted. Representatives of home infusion providers also complained that reimbursement is inadequate. We confirmed this same pattern of shifting Medicare patients from private practices to hospitals and other sites in its discussions with physicians. The IDF survey noted above also indicated some shifting of patients among healthcare locations.

4.4.5. Sample Calculations of Infusion Costs in Different Settings

Several groups have generated information on reimbursement problems in various settings. This section examines the costs of infusion services, as estimated for physician's offices, hospitals, and home healthcare.

4.4.5.1. Physician's Offices

With support from the PPTA, The Lewin Group performed a study in 2005 and early 2006 looking at reimbursement issues for physician's offices. Other source materials on infusion costs are also discussed. Regarding the Lewin study, Table 4-13 below is based on the case of a 3-hour, 32-gram infusion. Lewin also prepared costs for 5-hour and 8-hour infusions. The calculation in Table 4-16 shows a reimbursement shortfall of approximately $250 for this moderate-sized infusion. In this example, the loss is generated primarily by the difference between the CMS reimbursement and the average purchase cost of the IGIV for physician offices.

Table 4-16: The Lewin Group Comparison of Total CMS Payments to Total Reported Costs per Infusion in Physicians' Offices

Cost Component	CMS Payment 2006 [a]	Lewin Survey of Average Cost of Service
Pre-service	$69.00	$58.61
Clinical administration [b] [c]	$174.73	$201.04
Post-service	$0.00	$8.35
Average IGIV cost	$1,582.00	$1,807.00
Total	**$1,825.72**	**$2,075.00**
Unreimbursed Cost	**NA**	**-$249.27**

Source: The Lewin Group, 2006
[a] Based on Case 1: 3-hour infusion of 32 grams of IGIV.
[b] The Lewin Group reports that the clinical administration costs exclude payments for physician work. The above CMS rates include malpractice payments; the survey rates include malpractice payments assuming a 5-hour infusion. The costs do not include operating or ownership costs for infusion pumps.
[c] CMS commented for this study that the 2006 national allowance reimbursement rates are $77.31 for the first hour and $25.77 for the second hour for a 3-hour total of $128.95. Thus, using the CMS figures, the unreimbursed cost would be higher.

There also are other estimates of infusion cost services in physician's offices, infusion suites, and other settings. We also conducted our own informal survey of infusion costs. None of the other estimates, however, are sufficiently different than the above. In general, the other data suggest that many infusion providers are not as efficient as the physicians examined in the Lewin study and incur higher costs to provide infusion services.

The main themes demonstrated in the various infusion cost elements are as follows:

- Infusion providers spend a few hours in pre-infusion planning and preparations and in post-infusion monitoring. Additionally some time is needed for pre-infusion and post-infusion administrative work. While estimates vary as to exactly who and how much time is spent in pre- and post-infusion care, the labor costs for these stages in the various estimates are generally similar.
- The cost estimates are all based on a one-to-one nurse-to-patient ratio. While some providers, such as infusion suites, might capture some economies of scale when infusion nurses can monitor several patients, many infusion operations do not appear to capture such economies.

Many facilities perform occasional infusions or infuse one or two patients at a time. Further, infusion nurses are sometimes not integrated with the rest of the nursing staff and do not perform other nursing duties while monitoring patients.

- Many infusion providers find reimbursement inadequate because they cannot purchase IGIV at or below the reimbursement rate. Thus some providers take a loss on their IGIV purchases because they lack buying power or are not buying through large GPOs.
- Medicare reimbursement for physician and nursing services is modest but has not been changed except for CMS' recent add-on payment (e.g., the $69 shown in the Lewin study for reimbursement) to cover the time needed to acquire IGIV. In general, the CMS service reimbursement does not appear to be the source of recent complaints.

The CMS payment for IGIV infusion service is modest because it is not intended to do more than cover the costs of a basic infusion service. Unless an infusion provider can capture exceptional economies of scale, which are not evident at all in any infusion cost estimates, the CMS reimbursement for services is unlikely to be remunerative to the operation.

Under the AWP system, the Medicare reimbursement for the drug had the effect of subsidizing the provision of infusion services. With the lower ASP-based reimbursement, many physicians cannot or barely cover their drug costs (see Table 4-13). Further, Medicare reimbursement for the infusion service (which is not intended to cover more than basic service costs) does not offset or cushion potential losses from the drug purchase.

4.4.5.2. Non-Federal Hospitals

Hospitals are also reporting reimbursement to be inadequate to cover the costs of purchasing and administering IGIV. One hospital pharmacy provided a breakdown of its infusion costs, as shown in Table 4-17. The calculations display pharmacy costs for preparation of a 30-gram infusion and cover the variable costs of the hospital pharmacy staff. (The analysis does not explore the adequacy of coverage for physician and nursing services.) Those costs would be addressed in other reimbursement categories, such as the DRGs or physician and nurse charges allowed associated with Medicare Part A or B for patient treatment.

Table 4-17: Hospital Pharmacy Costs to Prepare an IGIV Infusion

Cost Category	CMS 2006 Reimbursement Rates	Actual Pharmacy Costs
Drug cost per gram	$60.24	$58.98
Total drug cost	$1,807.20	$1,769.40
Evacuated container	$0.00	$2.65
Needles (18g), label, seal, transfer set	$0.00	$2.50
Technician time (1 hour)	$0.00	$20.00
Pharmacist time (1 hour)	$0.00	$50.00
Total	$1,807.20	$1,844.55
Loss on Reimbursement	**NA**	**-$37.35**

Source: Information provided to ERG by large metropolitan hospital, 2006

In this hospital example, the reimbursement rate, as of the 2nd quarter of 2006, was sufficient to cover the cost of the IGIV but not the technician and pharmacist time associated with preparing the infusion. Thus, treating the hospital pharmacy as a separate cost center, these costs indicate that Medicare IGIV infusions generate a small loss for the facility for Medicare patients. As for the physician's office

case above, if a hospital cannot recover its full costs on the drug purchase (or narrowly capture those costs, as in this example), the infusion operation will be consistently unprofitable.

4.4.5.3. Home Infusion Providers

Home infusion providers also argued at the town hall meeting that Medicare reimbursement rates are inadequate under Part B. Under this provision, PI patients can receive IGIV infusions. In general, the argument on infusion costs vis a vis reimbursement is similar to that for infusion suites. In the home setting, however, the distribution of costs is different. There is no reimbursement for the labor components of the service although many facility overhead costs are reduced.

In general, the labor component of home infusion costs is somewhat higher than those for physician's offices and infusion suites, but other costs should be lower. For home infusions, there is generally one infusion nurse per patient so even the potential and modest economies of scale of infusion suite operations do not apply. The infusion nurse must also spend time traveling to an infusion site, so a 5-hour infusion with travel time often requires 6 to 7 hours of nursing time. Given the lower overhead of home infusion operations, however, overall home infusion costs are well below those of other infusion sites, such as hospitals.

At the town hall public meeting, one home infusion provider presented information showing that under Medicare Part B reimbursement (which applies only for PI patients) does not currently cover the acquisition cost of the drug. Depending on the home infusion company's contractual arrangements for IGIV supplies, smaller home infusion companies sometimes bear substantial losses simply to purchase IGIV. Medicare does not cover the additional non-drug costs of home infusion services.

For home infusion companies, Part D reimbursement for IGIV infusions is much more favorable. As noted elsewhere, home infusion company contracts with Part D prescription drug plans are generally based on AWP methodologies so the drug is reimbursed at a substantially higher rate than under Medicare Part B. Home infusion companies are generally able to recover their costs and profit from IGIV infusions under Part D.

The home infusion companies we interviewed indicated that that their companies cannot generally accept patients under Medicare Part B unless there is some supplemental arrangement for payment. The ASP-based Part B payment for IGIV is only sometimes sufficient to cover the cost of the drug. The home infusion company must obtain some other payment for the nursing services and the supplies or incur a loss for those costs as well. Thus, rather than accept long-term losses, home infusion companies generally do not accept Medicare-only Part B patients needing IGIV infusions.

In contrast, the same home infusion companies are providing service to many patients under Medicare Part D. CMS is not yet able to report on the number of IGIV patients served under Part D.

4.5. CONSEQUENCES FOR PATIENTS OF CHANGES IN PRESCRIBING OR ADMINISTRATION

IGIV access problems have generated reports of adverse health outcomes. Apart from the inconvenience for patients (and the potential dangers implied) of having the locations of healthcare sites changed, physicians and other healthcare providers have reported that the provision of IGIV therapy has been compromised. Given that the IGIV therapies in question are generally considered medically necessary, it must be presumed that there are sometimes adverse healthcare consequences from reductions in service. This section examines the consequences for patient health reflected in complaints and arguments on Medicare coverage.

In considering these reports, we generally lack a baseline or control group against which to compare the recent experiences of Medicare patients.

4.5.1. Physician and Patient Comments at the Public Meeting

A number of commenters at the town hall public meeting addressed the consequences for patients of IGIV access and reimbursement problems. These comments were summarized in a separate document (ERG, 2006). The comments suggest that some patients have suffered serious health problems or death due to difficulties in obtaining IGIV therapy.

One home infusion provider reported on the impact of Medicare reimbursement changes on his company's home infusion operation and the patients it covers. Table 4-18 presents the company's census of its Medicare patients. This firm's clients include patients covered by both Part B and Part D. According to the company's analysis, virtually all of these patients have had some difficulties with reimbursement – for instance, due to the burden of the co-pay requirements under Part D. He also noted that patients served under Medicare Part D might forego treatments due to the large co-pays, often then needing hospital stays.

Table 4-18: Summary of Medicare Patient Impacts of Medicare Reimbursement Changes from 2005 to 2006, as Reported by Home Healthcare Infusion Services Company

Patient Problem	Percentage of Patients	
	Part B	Part D
Switching IGIV product due to allocation issue	25	25
Switching IGIV product due to access issue	50	50
Change to administration location	100	100
Patients needing to become hospital inpatients to receive care	10	20
Patients needing to have Crescent Healthcare bring IGIV to the hospital to obtain dose	2	10
Patients receiving fewer treatments	5	10
Patients lower dosages	0	15
Patients with reimbursement problems	100	100
Patients with worsened health status due to any of the problems	10	35
Patients with payers who deny Part D coverage saying Part B applies (although it's a non-PI diagnosis)	0	20
Patients stopped IGIV therapy once Part D started	0	20
Total Medicare patient population (number)	10	101

Source: Rigas, 2006

Table 4-19 provides a brief summary of the comments made at the town hall meeting, with a separate tally of physician and patient comments. The summary shows considerable concern about reimbursement practices from both groups.

4.5.2. CMS Data on the Movement of Medicare Patients

CMS data depict the movement of patients from physician's offices to hospital outpatient care during 2005 and through the first quarter of 2006. Table 4-20 presents these figures. The data show that the number of IGIV patients receiving IGIV in physician's offices fell by 48 percent from the 4th quarter 2004 to the first quarter of 2006. The data also show growth over this period in the number of PI patients receiving infusions at home under Medicare Part B coverage – from 156 to 403 – although the total remains modest.

Table 4-19: Percent of Public Meeting Commenters Reporting IGIV Concerns

Commenter Complaint	Patients (66)	Physicians (21)	Other [a] (35)
Actual or possible cancellation/denial of treatment, due to limited allocations, difficulty procuring supply, and/or cost	58%	76%	60%
Changes in sites of service	55%	62%	46%
Concerns over quality of care or increased risk of infection in a different site of service	26%	43%	11%
Fewer treatments (prescribed or delayed by shortage)	38%	43%	37%
Reduced dosages	15%	24%	11%
Switching among products and/or specific products unavailable	36%	43%	34%
Specific reimbursement problems/complications due to insurance policies (Medicare or private) (patient or physician)	64%	71%	66%
Specific adverse health consequences experienced due to product availability, etc.	44%	38%	31%

Source: Compiled by ERG from town hall meeting comments
[a] Other includes nurses, pharmacists, manufacturers, patient relatives, and other uncategorized individuals.

During the period shown (2004 to 1st quarter of 2006), the total number of patients who received IGIV under Medicare Part B rose to 12,897 in the 1st quarter of 2005 but then fell to 12,241 in the 1st quarter of 2006. Presumably some of the patients moved to coverage under Part D, although there are no data available on the number of IGIV patients covered under Part D. Despite the migration of patients away from Part B during 2005, the total Part B patient coverage in the 1st quarter of 2006 was 1,513 patients larger than coverage in the 1st quarter of 2004 (10,728).

Table 4-20: Movement of Patients Receiving IGIV Between Physician and Hospital Outpatient

Location	2004-1	2004-2	2004-3	2004-4	2005-1	2005-2	2005-3	2005-4	2006-1
Home [a]	145	207	224	258	319	359	359	340	369
Hospital	4,873	5,026	5,155	5,431	6,610	7,157	7,439	7,621	8,166
Physician	5,710	5,907	6,114	6,430	5,968	4,904	4,110	3,733	3,706
Total	**10,728**	**11,140**	**11,493**	**12,119**	**12,897**	**12,420**	**11,908**	**11,694**	**12,241**
Home	1.4%	1.9%	1.9%	2.1%	2.5%	2.9%	3.0%	2.9%	3.0%
Hospital	45.4%	45.1%	44.9%	44.8%	51.3%	57.6%	62.5%	65.2%	66.7%
Physician	53.2%	53.0%	53.2%	53.1%	46.3%	39.5%	34.5%	31.9%	30.3%
Total	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**	**100.0%**

Source: CMS, 2006
[a] Refers to primarily PI patients receiving home infusion services under Medicare Part B.

4.5.3. Further Investigation of Patient Consequences from IGIV Access Problems

To investigate the issue of patient consequences further, we 1) discussed selected patient experiences with physicians who have commented on the IGIV access issues and 2) reviewed the latest survey evidence on patient access problems.

4.5.3.1. Selected Physician Interviews

Some patient advocacy groups have commented that individual patients have died or become seriously impaired due to lack of access to IGIV treatments. We interviewed four physicians who reported that a lack of IGIV access had contributed to individual patient deaths or serious impairment, or threatened to do so. The physicians were identified through their testimony at the town hall meeting,

through IDF, or by referrals from other physicians. Thus, they do not represent a random sample of physicians prescribing IGIV – they were selected because they were likely to be aware of problems with IGIV access. The IDF/AAAAI survey is discussed at the end of this section and provides a broader perspective on physician and patient experiences.

In reviewing the stories of individual patient difficulties, it should be noted that we lack means to independently confirm the stories offered. Both patient privacy concerns and the absence of complete information about the patients' health situation make the determination of causation uncertain. This type of anecdotal evidence is inherently unreliable due to the lack of any control group to compare experiences. The patients discussed are generally in a highly vulnerable condition and mortality rates would be high under any circumstances. To this concern we add that, as is noted, some of the negative patient outcomes are associated with periods when physicians were unable to monitor patients closely. Additionally, the patient histories are quite complex and we do not have any access to written reports on patient histories.

An Ohio physician provided IGIV therapies at his infusion clinic for about 30 Medicare and private insurance patients. With the change in reimbursement for physicians in January 2005, the physician reported that he immediately had difficulty covering the cost of IGIV for the Medicare patients. The physician continued to provide IGIV infusions for these patients for 10 months and then worked to transfer the patients to local hospitals. He generally continued to serve as these patients' doctor, but the infusions were now provided in the hospital.

The physician reported that it was both difficult and burdensome to transfer the patients to local hospitals, and that these efforts were not compensated. Also, the hospitals generally had limited extra IGIV allocations to accept new patients. Nevertheless, he was eventually able to transfer his patients. He noted that Medicare billing for these patients in the hospital setting was several times as large as that for his own infusion clinic.

In the course of the transfer process, at least two patients did not receive their normal infusions for two or more months. One patient suffered from chronic lymphocytic leukemia and the other from common variable immune deficiency. The patients were elderly and the exact cause of the interruption in therapy is not known. [Other physicians have noted that patients often miss infusions when they leave the hospital due to the difficulty and length of the process needed to obtain coverage for patients under home infusion services.] Both patients contracted pneumonia and died.

A neurologist in Texas reported that reimbursement-related problems had contributed to health problems for at least four different patients. The neurologist reported that she is unable to provide infusions to Medicare patients in either her private practice or at area hospitals. She stated that the reimbursement was so poor that she could not cover costs for providing therapy and instead, incurred large losses, some as large as $25,000 per patient.

Also, she has found that the local hospital sometimes will only infuse patients with a product that some patients cannot tolerate due to the sucrose levels. The hospital is very reluctant to buy Gamunex, which is substantially more expensive but does not include sucrose. This limitation on product choices has contributed to the infusion difficulties.

The neurologist described conditions for two patients, neither of whom had been able to receive infusions for several months. Reimbursement-based difficulties for physicians' office and hospital care apparently have prevented these patients from receiving infusions. One patient suffers from progressing paralysis of his diaphragm and IGIV infusions would help him to continue breathing. A second patient suffered from stiff-man syndrome and recently passed away. The neurologist reported that this patient could probably have survived for some time with continued infusions. She reported that patients such as

these deteriorate and, at some point, can no longer be brought back to health. The neurologist felt that these patients' health in particular had been affected by Medicare reimbursement problems.

The neurologist reported on two other patients whose deaths were influenced by the lack of IGIV infusions. The patients suffered from myasthenia gravis and CIDP. Their conditions deteriorated during periods when either no infusions could be provided or the available IGIV product was unsuited to them.

Another Texas neurologist also reported difficulties in getting IGIV infusions for patients. The neurologist stated that none of his patients had died due to lack of IGIV access but that reimbursement issues were having an adverse effect on the continuity of care. This neurologist noted that in September 2006 his hospital had instituted a strict protocol for use of IGIV that had restricted much of the off-label use of the product. He judged that the protocol was a response to losses on Medicare reimbursement for IGIV as well as some existing financial problems at the institution. At the time the protocol was implemented, he had approximately 8 to 10 Medicare-only patients. As a result of the hospital protocol, he transferred all of these patients to other therapies. In some cases the change was successful. Other patients, however, did not respond to the alternatives and he was continuing to seek more alternatives. He judged that Medicare patients in general were having the greatest difficulty in obtaining IGIV therapy.

He also described a patient with CIDP who was not able to obtain IGIV while the disease was under partial control. Alternative therapies were not effective and his condition deteriorated. He developed other medical complications, including diabetes mellitus and recurrent Guillan-Barre, which was caused by West Nile Virus and secondary poliomyelitis. The doctor was able to treat the patient with IGIV and this therapy was sufficiently successful to remove the patient from an artificial respirator. The patient remains very weak, however, and the doctor reports that he cannot provide repeated IGIV treatments.

A pediatric immunologist in Western New York reported that he was unable, due to inadequate reimbursement, to continue to treat Medicare patients in his private practice and has had to transfer them all to area hospitals. The transfer process was difficult for the physician, who had limited resources to work on placing patients elsewhere. It was also difficult for the hospitals: the hospital physicians were not always able to accept new patients although the hospitals were obligated to accept the patients.

Patients were also adversely affected. In the transfer process, some patients did not receive infusions in a timely fashion. One patient got pneumonia and another patient can no longer walk. In general, with missed or delayed infusions the physician noted that patients got more infections. Eventually, the patients have been able to receive infusions at the area hospitals.

The time needed for infusions lengthened considerably in the hospital setting, partly because hospitals were uncertain how quickly patients could be infused or because the hospitals used very conservative treatment protocols. This physician felt that his experience was quite representative of that of many other immunologists.

In the course of the other physicians' interviews during this study, physicians indicated that some health problems can be anticipated for these patients if infusions are missed or delayed. The half-life of IGIV is 21 days, meaning that half of the immune system protection has expired in that time period. Thus, normal infusion frequencies are every three to four weeks. Patients who have not received IGIV for three months are assumed to be at their baseline condition, i.e., without any IGIV remaining in their system. For PI patients, this might mean essentially no immune system protection. In these circumstances, the patient's vulnerability to infections would be quite high. Nevertheless, there are also immune deficient patients that can go untreated for some time and not get sick. That is, patient susceptibility to infection is highly variable.

The frequency of transition problems for patients moving between care settings is possibly high. One immunologist indicated that when his PI patients are released from the hospital they typically miss at least one infusion during the transition, and it is not unusual for patients to miss two or even three. The delays occur despite the best efforts of physicians and hospital personnel to place patients with home infusion companies. It generally takes more than a month for the hospital staff to interact with potential infusion companies and for the companies to review the patient's history and insurance coverage to determine if they can accept the patient.

On this theme of transition difficulties, the National Home Infusion Association (NHIA) surveyed hospital discharge nurses to determine how Medicare Part D has affected their job. This study is not specific to IGIV infusions and refers to all types of home infusion services. It is most focused on the problem of maintaining continuity of immediate infusion services, such as antibiotics, and on the difficulties of placement for dual-eligible (Medicare and Medicaid) patients. The NHIA study concluded that Part D has generated considerable complications for discharge nurses and that delays in releasing patients from hospitals are quite common. Thus, discharge nurses spend considerable time to identify home infusion providers who can accept specific patients and may be reimbursed under their contracts with PDPs. NHIA's study found the problem to be particularly problematic for dual-eligible patients. The delays often cause patients to spend an additional day or more in the hospital (NHIA, 2006).

4.5.3.2. Survey Data on Patient Health Problems Related to Access

Turning to patient illnesses, there are two surveys that describe health effects for a sample of the affected patient population. A recent IDF-AAAAI patient survey (2006) shows difficulties for PI patients due to interruptions or withdrawal of IGIV treatments. The survey covered slightly more than 1,000 PI patients, and distinguished experiences of Medicare and non-Medicare patients. The relevant results from the IDF-AAAAI survey are described further below.

IDF- AAAAI measured the share of IGIV users whose IGIV therapy was apparently affected by either reimbursement or other access problems. They found that 26 percent of Medicare patients and 10 percent of non-Medicare patients suffered negative health effects due to problems getting or paying for IGIV. Table 4-21 below presents the range of health effects reported. Among those reporting health effects, a fairly wide array of problems arose.

Table 4-21: Health Effects Among Patients Reporting Problems Obtaining or Paying for IGIV Therapy

Health Effect	All Patients		Patients Under 60 Years of Age	
(More Than One Answer Accepted)	Medicare	Non-Medicare	Medicare	Non-Medicare
Hospitalized	4%	1%	5%	1%
More infections	21%	6%	27%	6%
Increased antibiotics	19%	6%	24%	6%
New side effects	11%	4%	17%	4%
Pneumonia	7%	2%	11%	1%
Bronchitis	14%	3%	19%	3%
Other [a]	19%	6%	26%	5%

Source: IDF, 2006b

[a] Includes joint pain, fatigue, sinus problems, weight loss, and other unspecified effects.

Note: The total number of patients responding to the health effects question was 255 Medicare patients and 391 non-Medicare patients. Among patients under 60 years of age there were 117 Medicare patients and 343 non-Medicare patients. The health effects are self-reported by the patients.

The IDF-AAAAI data do not provide a control group that would indicate the number of health problems that a population of these patients might normally expect in a year. IDF did, however, calculate the health effects separately for patients less than 60 years old in order to test the effect of age on the health outcomes. In fact, the younger patients were generally more likely to have experienced health problems than the overall population.

The IDF- AAAAI survey provides an important perspective on the frequency of patient health problems. In the IDF-AAAAI survey, none of the physicians reported a death among their patients that was attributed to IGIV access problems. Ten percent of the immunologists reported one hospitalization among their patients and 3 percent reported "several" hospitalizations. Additionally the immunologists reported additional medical visits and increased telephone contacts with office staff. Nevertheless, the absence of any deaths indicates strongly that there are not much more widespread difficulties than the relatively few, albeit very serious, patient histories described above.

We lack equivalent data to the IDF surveys for neurology patients. Where hospitals have implemented use protocols, they generally will give a lower priority to off-label uses (e.g., neurology uses), and some of the physician commentaries indicate that neurology patients are being excluded from treatment. Thus, this group of patients and particularly Medicare neurology patients are likely to be incurring some reductions in IGIV therapy.

4.6. CONCLUSIONS

The data presented here and in Sections 2 and 3 indicate that both Medicare reimbursement and IGIV supply shortfall contribute to patient access difficulties. Given the fact that access problems have been reported more frequently for Medicare beneficiaries, there is some contribution of Medicare reimbursement to the access problems. Further, reimbursement issues have been preeminent when discussing patient problems with physicians and with home infusion services. In contrast, the IDF survey of hospital pharmacy directors suggests that hospitals are more likely to have availability difficulties.

As described above and expressed at the town meeting, IGIV reimbursement levels appear inadequate in some circumstances to cover costs. Physician's offices and hospital outpatient infusion clinics receive their normal reimbursement for infusion services, but, in some cases, do not recover the full IGIV purchase costs. The shortfall in IGIV purchase costs discourages these providers from offering infusions. Under the previous AWP-based reimbursement for IGIV, the margin on IGIV purchase offset the costs for the provision of services and provided a profit for operations. With the institution of the ASP methodology, IGIV infusion services for Medicare patients are sometimes unprofitable. In 2005, there was exceptional patient migration among IGIV infusion providers caused principally by reimbursement-change-induced closures of infusion services in physician offices. In interviews with infusion providers, reimbursement was the principal reason given for the need to relocate patients to other providers.

For home infusion companies, Medicare has never reimbursed for the infusion service. The switch from AWP- to ASP-based reimbursement for some Medicare patients eliminates the drug purchase margin that covered the cost of infusion services and profits. As a result, home infusion companies are not generally providing services to PI patients with Part B reimbursement levels. They are providing infusions to Part D patients under their contracts with PDPs, which incorporate AWP pricing.

Medicare patients reported more health problems due to lack of IGIV access than private insurance patients, in surveys conducted by IDF. The IDF survey data covers primarily patients with immune deficiency diseases. Equivalent data for neurology patients, some of which might rely on IGIV therapy, are not available. Several deaths are said to have been influenced by patient difficulties in obtaining IGIV therapy, including both immune deficiency and neurology patients.

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