

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.