

*Specialty  
Injectables*

**DRUG TREND**

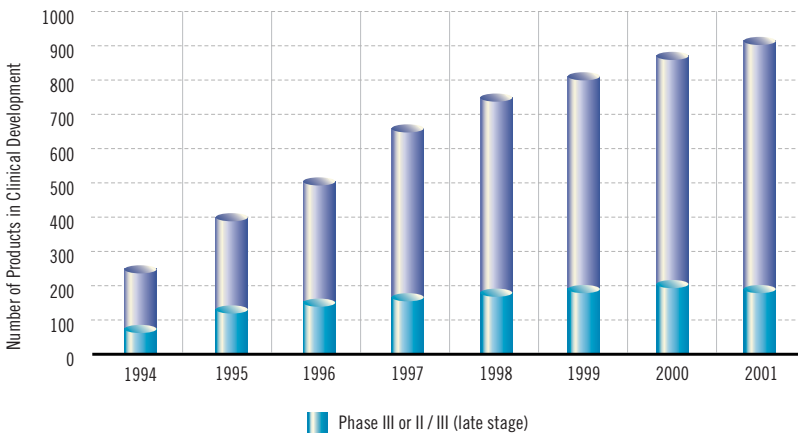
*2002 Report*

# The Growing Costs of Specialty Injectable Drug Products

Each year, more people use specialty injectable drugs as part of their medication therapy. In 2002, more people received specialty injectable products through their pharmacy benefits. This trend was clearly evident in Express Scripts' specialty-care pharmacy, which dispensed 90 percent more prescriptions in 2002 than in 2001.

U.S. revenues for the specialty pharmacy market, estimated at \$22 billion in 2001, are expected to increase by 20 percent annually.<sup>31</sup> The expanding biotechnology industry is a significant driving force behind this growth. In 2001, over 900 products targeting more than 200 diseases were making their way through biotechnology drug company pipelines (see Figure 10).

Figure 10  
**Biotechnology Pipeline**



Source: Goldman Sachs. Healthcare: Biotechnology. January 14, 2003: Page 8

Another factor driving growth of the injectable market is the lack of generic products. Although the FDA has an established process for approving generic equivalents of traditional drugs, the agency currently has no comparable process for allowing generic versions of biotech drugs to come to market.

With the typical injectable drug costing well over \$1,000 per month, payers recognize the impact that specialty injectables can have on both medical and pharmacy benefits. The first step in addressing specialty drug cost is to establish a clear definition for this category. Currently, typical inclusion criteria include the annual drug cost, whether the product is injectable or infused, and whether it is administered in the home or a physician's office. Some plans also consider high-cost oral products, such as Tracleer<sup>®</sup> or Gleevec<sup>™</sup>, as specialty drugs.

31 Ransom J, Rettig T. Specialty Drug Distribution. Raymond James and Associates. July 16, 2002. Available at: <http://170.12.99.3/researchpdf/IDRU071602RPT.PDF>. Accessed March 25, 2003.

To manage the specialty cost effectively, a plan sponsor must consider drugs covered under both pharmacy and medical benefits. The medical benefit is of particular concern because of the unique coding structure used for medical claims. Drug-specific data is rarely available in medical claims; consequently, it is difficult for a plan to measure the drug spend or determine for which drugs they are paying. Many plans have begun moving these drugs to the pharmacy benefit, in part to determine their specialty drug cost. Others have created a new benefit called an “Injectable” benefit. Finally, others are looking for technological solutions to incorporate medical claims data and drug-specific information.

Today, the most common method of addressing the costs of specialty drugs is through discounted pricing via specialty pharmacies. These pharmacies often offer discounts in return for some promise of increased volume. Plans, on the other hand, must limit their members’ choices in order to steer them to these providers. Specialty pharmacies frequently offer additional patient support through education and high-touch customer service. Specialty pharmacies have the ability to bill both pharmacy and medical benefits, yet plans struggle to consolidate the data across their network to measure total specialty cost.

Formularies have proven to be an effective way for plans to lower oral drug costs. Except in the class of growth hormones, however, only a few therapeutic substitutions now exist in the specialty drug category from which to build formularies and leverage manufacturer discounts. The drug pipeline shows several upcoming opportunities for competition to existing drugs, however. Plans should actively monitor these developing drugs in preparation for adopting specialty formularies.

Clinical programs, such as prior authorization and step therapy, can affect utilization for some specialty drugs. Drug therapies for RA, MS and hepatitis C all are candidates for these types of programs. Additionally, some patients may respond to disease management programs.

Increasingly, plans are looking to pharmacy benefit managers (PBMs) to help manage the specialty drug cost. PBMs have the ability to build networks of specialty pharmacies and leverage discounts. Additionally, PBMs can offer efficient, cost-effective mail service for certain specialty drugs. Overall, PBMs have proven tools and methods to lower plan costs. Finally, as PBMs address the issue of medical claims management, they will be in a position to integrate specialty drug data across both benefits, allowing for a complete management solution.

The following sections provide an overview of the top therapeutic classes that currently drive the injectable drug market. One notable exception is a general overview of cancer therapies, which contribute significantly to healthcare costs. While certain therapeutic classes related to cancer treatment can be found in this section of the Report, a more detailed discussion of cancer and its treatments can be found in Appendix A. It is important to note that the products mentioned in this section may be covered under either the medical or the pharmacy benefit, and in some cases, both.

## Fertility Regulators

### Primary Use: Infertility

Infertility is defined by the World Health Organization as the inability of a couple to achieve conception or bring a pregnancy to term after one year or more of regular, unprotected sexual intercourse. Primary infertility is the inability to conceive a first child and secondary infertility is the inability to conceive a second or subsequent child. One out of 10 couples worldwide experience primary or secondary infertility.<sup>32</sup> Infertility therapy is now highly successful, with pregnancy rates obtained with most treatment comparable to natural pregnancy rates.

Current drugs to treat infertility include chorionic gonadotropin (hCG), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Each of these drugs plays a specific role in the reproductive cycle. FSH stimulates the development of follicles in the ovaries, which ultimately lead to fully developed eggs. FSH is typically given with LH, which is responsible for final maturation of the developing egg; hCG triggers ovulation, so one of these products is given after FSH and LH have had time to work. Another class of products known as gonadotropin antagonists is used to control the ovulation cycle, which is important when exact timing is necessary for other infertility therapies.

Infertility treatments can be either human-derived or recombinant. Human-derived products are made from the urine of postmenopausal women, while recombinant products are produced using DNA technology. Most of the medications are self-injectable in nature. The following table lists some of the significant infertility products.

Table 12  
Selected Infertility Products

| DRUG NAME  | PRODUCT TYPE            | METHOD OF ADMINISTRATION |
|------------|-------------------------|--------------------------|
| Gonal-f™   | Recombinant FSH         | Subcutaneous             |
| Follistim® | Recombinant FSH         | Subcutaneous             |
| Pergonal®  | Human-derived FSH/LH    | Intramuscular            |
| Repronex®  | Human-derived FSH/LH    | Subcutaneous             |
| Lupron®    | Gonadotropin antagonist | Intramuscular            |
| Ovidrel®   | Recombinant hCG         | Subcutaneous             |
| Antagon™   | Gonadotropin antagonist | Subcutaneous             |
| Bravelle™  | Human-derived FSH       | Subcutaneous             |
| Cetrotide® | Gonadotropin antagonist | Subcutaneous             |

**Pipeline:** The pipeline for infertility drugs is relatively quiet. Most activity involves making existing products easier to take. The manufacturer of Gonal-f™ is developing a microencapsulated form of the drug that is designed to decrease the frequency of injections. Other companies continue to find ways to further purify their compounds, thereby reducing the risk of adverse reactions. Oral versions of these products are years away. Luveris®, which contains FSH and luteinizing hormone-releasing hormone (LHRH), is currently under review at the FDA.

32 Department of Reproductive Health and Research (RHR), World Health Organization. Infertility. October 2002. Available at: <http://www.who.int/reproductive-health/infertility/index.htm>. Accessed March 26, 2003.

## **Beta-interferons**

### **Primary Use: Multiple Sclerosis**

Multiple sclerosis (MS) is a progressive disease of the central nervous system. It is an autoimmune disease in which tissues surrounding the nerves of the body are damaged. This results in an inability of the nerves to communicate with one another, and leads to symptoms such as tremor, loss of balance and visual disturbances. MS has no cure.

There are four major types of MS: Relapsing-Remitting, Secondary-Progressive, Primary-Progressive and Progressive-Relapsing. Relapsing-Remitting MS is the most common form, occurring in approximately 75 percent of patients. This type of MS is characterized by intermittent attacks, or relapses, of MS symptoms followed by periods of near-normal functioning. About half of the patients with Relapsing-Remitting MS progress to Secondary-Progressive MS, in which the symptoms of MS may wax and wane, but the disease progresses overall. In contrast, Primary-Progressive MS patients experience a slow but continuous worsening of MS symptoms without periods of remission. The final type of MS, Progressive-Relapsing, is noted by immediate disease progression with occasional periods of remission.

The current market basket of drugs used to treat MS consists of Copaxone® and Novantrone® as well as the beta-interferons. In 1993, Betaseron® was the first beta-interferon approved, followed in 1996 by Avonex® and in 2002 by Rebif®. All of the beta-interferons are indicated for the treatment of Relapsing-Remitting MS. Avonex® is administered as a once-weekly intramuscular injection, while Betaseron® is administered every other day and Rebif® three times per week. In 1997, Copaxone® was introduced to the market. Copaxone® is not an interferon but instead works by blocking nerve-damaging cells. Novantrone® has been on the market for many years as an anti-cancer drug, and in 2000 it received approval for MS. Due to its side effect profile and monitoring requirements, it is typically reserved for more severe cases.

**Pipeline:** Perhaps the most promising compound in the pipeline for MS is Antegren™ (natalizumab). Antegren® is the first monoclonal antibody being developed for MS; it provides a different mechanism of action than currently available therapies. Because of its unique mechanism of action, Antegren® can be used for patients who have not responded to other MS therapies, and it can be used in combination with a currently available treatment. An oral version of Copaxone® is under development, but initial studies did not show a treatment benefit. Other drugs in development focus on the immune system and the source of inflammation, but they will not reach the market for a few years.

## **Interleukins**

### **Primary Uses: Selected Cancers and Low Platelets in Cancer Patients**

Interleukins are a group of proteins that play an important role in regulating some of the body's activities. Found within body cells, interleukins and other similar proteins are part of a family of chemicals called cytokines, which function as one of the body's messenger services. Cytokines carry important information between cells, instructing the cells to perform a certain function. For example, one cytokine may tell the body to increase the amount of cancer cells in a tumor, while another may be designed to decrease the number of platelets being manufactured by the body.

At least 27 different forms of interleukin have been identified in the body. They are named by number (interleukin-1, interleukin-2, etc.) and often abbreviated as IL-1, IL-2, and so on.

Drug therapy using interleukins is achieved either by increasing the amount of interleukins circulating in the body or by blocking their effects. The first interleukin product, Proleukin® (IL-2) was approved by the FDA in 1992 for the treatment of kidney cancer. Proleukin® works by assisting the body's own interleukins in attacking and killing cancer cells. It is typically administered in a hospital setting because of potential side effects. The second interleukin, Neumega® (IL-11) is approved for patients with low platelet counts following chemotherapy. Neumega® directly stimulates the development of platelets. It can be self-injected once daily until platelet levels return to normal, a process that usually takes 21 days or less. The third interleukin drug approved by the FDA does not enhance interleukin activity but instead prevents it. Kineret™ blocks the effects of interleukin-1, which is one of the prime causes of inflammation in rheumatoid arthritis patients. It is given as a self-injection on a daily basis. Therapy with Kineret™, unlike Proleukin® and Neumega®, is chronic in nature.

**Pipeline:** Significant research is taking place in the field of interleukins. Because there are so many potential sites of action (27 or more), identifying potential drug targets is important. Currently, at least 11 interleukin subtypes are under study for potential drug targeting. Diseases potentially treatable with these products include asthma, Crohn's disease, MS, lupus, psoriasis, dermatitis and many different forms of cancer. Despite this significant activity, no new interleukin drugs are expected on the market in the immediate future. Prestara™, a hormone-based drug with interleukin activity (but not a true interleukin), is a future candidate for approval.

## **Alfa-interferons**

### **Primary Use: Hepatitis C**

Like interleukins, interferons are natural proteins produced by the human body. They assist the body's other defenses in fighting off invading cells that can carry disease. Although interferons were discovered in the 1950s, the first was not approved for use until 1986. Because of their relatively non-specific effects, interferons are used in a wide variety of disease states. Three different forms of interferon are on the market today, and while they are all interferon molecules, they differ in their specific mechanisms of action and response to disease. Alfa-interferons, the first interferons introduced, are used for different types of cancer, hepatitis and genital warts. In 1993, the first beta-interferon was approved for the treatment of MS. A gamma-interferon, Actimmune®, was approved in 1990 for the treatment of a rare immune deficiency called chronic granulomatous disease. The remainder of this section will focus on alfa-interferon therapies.

The current alfa-interferon market consists of several products, although two newer products are receiving the most attention. The first alfa-interferons, Intron® A and Roferon®-A, were approved in 1986 for treating patients with hairy cell leukemia, a form of cancer. In subsequent years these products received additional indications for the treatment of hepatitis C and Kaposi's sarcoma, a cancer fairly common among AIDS patients. Intron® A and Roferon®-A are similar products, and both are produced using recombinant DNA technology. In 1989, the interferon Alferon N® was approved for the treatment of genital warts. Alferon N® differs from Intron® A and Roferon®-A in

that it is produced using human white blood cells rather than by recombinant DNA technology. A fourth alpha-interferon, Infergen<sup>®</sup>, was approved in 1997 for the treatment of hepatitis C. Infergen<sup>®</sup> differs from the aforementioned products in its chemical structure, so it is not a true alpha-interferon but it is very similar.

While interferons were used modestly with some success in different patient groups, their use grew dramatically with the approval of Rebetrone<sup>™</sup> in 1998. Rebetrone<sup>™</sup> combines Intron<sup>®</sup> A with the oral antiviral drug ribavirin for the treatment of hepatitis C. It was an immediate success due to the improved response rates seen with this combination therapy. The hepatitis C market surged in the following years as more patients were diagnosed and started on therapy. In 2001, a new form of Intron<sup>®</sup> A was introduced. Called PEG-Intron<sup>®</sup>, it offers similar effectiveness to Intron<sup>®</sup> but fewer injections per week (one versus three). PEG-Intron<sup>®</sup> was joined by a competing product, Pegasys<sup>®</sup>, in 2002. Pegasys<sup>®</sup> is also administered once weekly.

**Pipeline:** The interferon pipeline largely focuses on expanding the uses of existing drugs rather than developing new drugs. For example, alpha-interferons are being studied for the treatment of several cancers, including melanoma, non-Hodgkin's lymphoma and chronic myelogenous leukemia (CML). Research with gamma-interferon focuses on cystic fibrosis, asthma and ovarian cancer. A new class of interferons, the omega-interferons, is in early stages of development for hepatitis C and cirrhosis. One specific omega-interferon is being designed to target the liver, which may lessen the side effects seen with other interferons. Perhaps the most unique drugs in development are interferon antagonists. These anti-interferon drugs are expected to be tested for diseases, such as Crohn's disease and psoriasis, in which the overexpression of interferons is detrimental.

## Heparins

### Primary Use: Prevention of Blood Clots

Heparin products are also known as anticoagulants. Their primary role is the prevention and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT occurs in the deep veins of the body, most often in the veins of the legs. It can be caused by a variety of conditions, such as inactivity, obesity or trauma. Each of these conditions includes periods of decreased venous blood flow. When this occurs, the body starts to initiate its coagulation process, which ultimately leads to the formation of a blood clot. Most often a blood clot stays in the location where it is formed, such as the leg, resulting in localized pain and discomfort. However, sometimes a blood clot breaks loose from its location and enters the general circulation. If the clot reaches the arteries of the lung, it may result in a PE, which can be fatal.

Heparin is the standard of care for acute treatment of DVT and PE. The effects of heparin have been known for almost a century. Heparin binds to a specific mediator in the coagulation process and works quickly to dissolve blood clots. It is usually given by intravenous infusion in a hospital setting. Heparin is also widely used for the prevention of DVT, as a subcutaneous injection. However, heparin therapy requires intense monitoring, so opportunities for patients to self-inject heparin remained limited until the 1990s, when heparin therapy was enhanced by the approval of Lovenox<sup>®</sup>, the first low-molecular-weight heparin. Lovenox<sup>®</sup> and subsequent similar products

contain a smaller piece of the heparin molecule, and they are administered as self-injections. Low-molecular-weight heparins are equally as effective as heparin for the treatment of DVT and PE, and they provide a safety benefit over regular heparin because typically monitoring is not required. Two products, Lovenox® and Innohep®, are approved for the prevention and treatment of DVT, while two additional products, Fragmin® and Arixtra®, are approved for the prevention of DVT. Technically, Arixtra® is not a heparin, but it works similarly to the low-molecular-weight heparin products.

**Pipeline:** Currently, research focuses on oral products that could eventually replace the injections now required for the treatment of DVT. Warfarin is a widely available oral anticoagulant, but it takes a few days to work, which is why heparin and warfarin are given together to many patients who have experienced DVT. The product closest to market is Exanta™, which is a direct thrombin inhibitor being studied for both prevention and treatment of DVT. Other products in the pipeline are designed to target specific factors that cause coagulation, and several companies are designing oral versions of heparin itself.

## LHRH Analogs

### Primary Uses: Endometriosis and Prostate Cancer

LHRH is an abbreviation for luteinizing hormone-releasing hormone, and an LHRH analog is a drug that mimics the effect of LHRH in the body. Given on a short-term basis, LHRH increases the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are the hormones responsible for increasing the levels of testosterone (in males) and estrogen (in females). As a result, LHRH analogs are often used as part of an infertility regimen in women. However, if LHRH is given on a more chronic basis, levels of FSH and LH are reduced, resulting in low levels of testosterone or estrogen. Conditions in which low levels of FSH and LH are desirable include prostate cancer, endometriosis and central precocious puberty. Because LHRH analogs decrease the levels of sex hormones in the body, they have the effects of chemical castration in males and cessation of menstruation in females. These effects are reversible upon discontinuation of therapy.

The most commonly used LHRH analog is Lupron®. Lupron® comes in many different formulations, including a subcutaneous injection and several long-acting, or depot, formulations that can be given in intervals of up to 4 months. An implanted version, called Viadur®, is active for one year. A second LHRH analog, Zoladex®, is also available as a subcutaneous injection in 1-month or 3-month depot formulations. Zoladex® is commonly given with oral chemotherapy drugs as part of a prostate cancer regimen.

**Pipeline:** Significant new drug development does not appear to be taking place in the area of LHRH analogs. The primary focus will continue to be designing delivery systems that are effective and long-acting, thereby decreasing the number of injections needed over a period of time.

## ***Tumor Necrosis Factor Inhibitors***

### **Primary Uses: Rheumatoid Arthritis, Crohn's Disease and Psoriasis**

Part of the body's immune system, tumor necrosis factor (TNF) is a protein that helps stimulate the body's response to infection or disease. It gets its name because one of its first known activities was the breakdown of certain cancer cells. Since its initial discovery, TNF has been implicated as a cause of cachexia, which is the loss of lean body mass in patients with cancer, and as an inflammatory mediator in diseases such as rheumatoid arthritis (RA), Crohn's disease and psoriasis. Joint destruction can also occur when TNF levels are high. Drug therapy is designed to target circulating TNF and block its effects.

Three TNF-inhibitors are currently on the market. They differ in chemical composition, approved uses and methods of administration. The first anti-TNF drug was Remicade®, approved by the FDA in August 1998 for the treatment of Crohn's disease. Since its initial approval, Remicade® has received approval for use in RA. It is given in a physician's office by intravenous infusion every 4 to 8 weeks depending on the severity of the disease. The FDA approved the second TNF-inhibitor, Enbrel®, in November 1998. First approved for use in RA, Enbrel® has since added additional indications for juvenile RA and psoriatic arthritis, which is arthritis caused by the skin disease psoriasis. It is self-administered twice weekly by subcutaneous injection. Remicade® and Enbrel® received additional competition at the end of 2002 when the FDA approved Humira™ for the treatment of RA. Like Enbrel®, Humira™ is a self-administered subcutaneous injection. However, Humira™ is given less frequently than Enbrel®, with an every-other-week dosage regimen.

**Pipeline:** The pipeline for TNF-inhibitors is quite large, in both the number of products and the number of new uses for existing products. Each of the currently marketed TNF-inhibitors is being studied for effectiveness in psoriasis, a disease with few effective treatment options. Remicade® is being studied for asthma to see if the anti-inflammatory effects seen in RA and Crohn's disease can be applied to a respiratory disease. Efforts are also under way to simplify dosage regimens. Once-weekly injections are being studied for Enbrel®. A subcutaneous version of Remicade® that is in development would allow self-injections. On the new drug front, the closest product to market is likely CDP-870, which offers monthly subcutaneous dosing. Other unique drugs in development include oncept, a TNF-binding protein; and DPC 333, an oral therapy to inhibit an enzyme that produces TNF.

## ***Colony Stimulating Factors***

### **Primary Use: Increasing White Blood Cells in Cancer Patients**

White blood cells called neutrophils are the body's primary defense against infections. A low number of neutrophils in the body is called neutropenia. Neutropenia is a serious condition, because even the smallest infection can cause serious complications or even death. The condition occurs most often in people receiving chemotherapy for cancer and in bone marrow transplant recipients. Cancer chemotherapy drugs are so strong and toxic that they often destroy healthy cells in addition to the cancerous cells. During the time that the body takes to regenerate healthy white cells, patients are at the greatest risk of infection. Many years ago the only course of action was trying to prevent infections by administering multiple antibiotics while waiting for the body to regenerate new white blood cells from the bone marrow. In recent years, new therapies that

directly stimulate the bone marrow into producing more white blood cells were developed. These therapies, called colony stimulating factors, reduce the risk of serious infections, allowing patients to stay on their scheduled cancer chemotherapy regimens.

Three colony stimulating factors are currently on the market. The first two, Neupogen® and Leukine®, were approved in 1991, and the third, Neulasta™, in 2002. Neupogen® and Neulasta™ contain the same active drug but differ in their methods of administration. Neupogen® is given on a daily basis, either subcutaneously or intravenously, until the patient's white blood cell count is at an acceptable level, which can be up to 2 weeks for chemotherapy patients and even longer for bone marrow transplant patients. A long-acting form of Neupogen®, Neulasta™ is given by subcutaneous injection at the start of each chemotherapy cycle. Leukine® is a slightly different form of colony stimulating factor used for specific types of cancer and in bone marrow transplantation. It is given primarily as an intravenous infusion, but it can also be given subcutaneously.

**Pipeline:** Because neutrophils are the body's natural defense against infection and because some current therapies specifically target neutrophils, opportunity for new drug development is limited. It is possible that new therapies could further enhance the delivery of drugs to the body or perhaps complement existing therapies, but no such therapies are in advanced clinical trials.

### ***Erythroid Stimulants***

#### **Primary Use: Increasing Red Blood Cells in Patients with Kidney Disease or Cancer**

The body manufactures two different types of blood cells: white blood cells, some of which are described above, and red blood cells (erythrocytes), which have the primary purpose of carrying oxygen from the lungs to the rest of the body. Red blood cells are generated in the bone marrow, and their production is stimulated by a protein called erythropoietin. When the circulating amount of red blood cells is decreased, anemia results. Conditions that can cause anemia include kidney disease and chemotherapy for certain kinds of cancer. If the body's own bone marrow cannot generate enough new red blood cells to replace those lost by disease or drugs, a blood transfusion is usually necessary. Research done in the 1980s led to the development of an erythroid stimulant — recombinant erythropoietin — which is used to supplement the body's own erythropoietin and limit the occurrence of anemia and the resulting need for blood transfusions.

The current recombinant erythropoietin market consists of three products, two of which are the same molecule. The first product, Epogen®, was approved in 1989 for use in patients with advanced kidney disease, including dialysis patients. The company that discovered and developed Epogen® then licensed certain rights of the product to another company, and the drug was brought to market in 1990 as Procrit®, which is used for anemia related to cancer chemotherapy. Even though the two different products, Epogen® and Procrit®, are being marketed for different diseases, the active ingredient, erythropoietin, is the same in both products. In 2001, a next-generation erythropoietin product, Aranesp™, was brought to market for anemia caused by either kidney disease or chemotherapy. Aranesp™ is a slightly modified version of erythropoietin that is approved for less frequent dosing than Epogen® and Procrit®.

**Pipeline:** Opportunities for new drugs to compete in the class of erythroid stimulants may prove difficult, as existing therapies provide supplemental erythropoietin to the body's own stores of the protein. However, research is being done on compounds that enhance the delivery of erythropoietin to the cells that need it. One such method of enhancing delivery is through gene activation. Currently, supplemental erythropoietin is produced by inserting the gene for human erythropoietin into the cell of an animal, where it is grown for mass production. Gene activation takes place within the human cell by “turning on” the gene to produce more erythropoietin. Another method of erythropoietin delivery, in very early stages of development, uses inactive erythropoietin that is injected, stored in the body and then activated by an oral drug.

## ***Growth Hormone***

### **Primary Use: Growth Hormone Deficiency**

Growth hormone is secreted by the pituitary gland. When it reaches the liver it stimulates the production of another hormone, called insulin-like growth factor one (IGF-1), which is responsible for the effects typically associated with growth hormone. Growth hormone deficiency occurs when the production of growth hormone is disrupted. Initially, growth hormone was obtained from human cadavers. That practice was stopped in the 1980s, when therapy was shifted to recombinant versions of human growth hormone. Therapy with growth hormone can be divided into three categories: patients with documented growth hormone deficiency, patients with short stature due to a concomitant disease and patients with muscle wasting due to AIDS.

The first recombinant growth hormone, Protropin®, was approved in 1985 for use in children with growth failure. Protropin® was soon followed by several products (Humatrope®, Nutropin®, Genotropin®, Norditropin® and Saizen®). All of these products are approved for use in children with growth hormone deficiency and some are also approved for use in adults. An additional growth hormone product, Serostim®, was approved by the FDA in 1996 for the treatment of AIDS wasting, a disorder in which the body uses lean muscle mass instead of stored body fat for energy. All growth hormone products can be self-administered as subcutaneous injections, and most are given on a daily or almost-daily basis. Nutropin® is also available as a long-acting depot formulation, which reduces the number of injections to one or two per month.

**Pipeline:** The development of new drugs to treat growth hormone deficiency focuses on alternative delivery systems. At least two oral versions of growth hormone are being developed, as is a nasal version, although each is a number of years from the market. A fourth product contains growth hormone attached to the protein albumin. This design may allow for less frequent dosing.

## ***Intravenous Immune Globulin (IVIG)***

### **Primary Use: Immunodeficiency Caused by Genetics, Cancer or HIV**

IVIG products are used for immunodeficiencies, conditions in which the body's immune system is not working properly. The immune system is the body's defense against infection, and it consists of many different types of cells and proteins. When these cells and proteins fail to work properly, the body is more susceptible to infections. The most common immunodeficiency is caused by a genetic defect that is usually passed from parents to children. Immunodeficiencies present at birth are called primary immunodeficiencies. More than 70 different forms of primary immunodeficiencies, with varying levels of severity and incidence, have been identified to date.

IVIG is a therapy for patients with immunodeficiencies caused by a lack of antibodies. Antibodies are large proteins, also known as immunoglobulins, which attach to foreign substances, such as bacteria, and "hold" them until another immune cell, the macrophage, destroys them. Without enough circulating antibodies, persons with an immunodeficiency are more susceptible to even the mildest infections. Something as simple as a cold can be very serious to a person with an immunodeficiency. IVIG is given to these patients to provide a higher level of circulating antibodies that work to prevent future infections. IVIG is made from human blood that has been purified to prevent contamination. Typically, it is administered by intravenous infusion, either at home or at a medical clinic. Therapy with IVIG is repeated every 3 to 4 weeks for the patient's lifetime. IVIG products include Gammagard®, Venoglobulin®-S, WinRho SDF® and Gamimune® N. Each of these products is a unique formulation; not all have the same FDA-approved uses.

**Pipeline:** Current research in the area of immunodeficiencies focuses on both drug and non-drug therapies. Gene therapy is the most active area of research. Because a primary immunodeficiency is the result of a genetic defect, research is being done to see if inserting healthy genes into the cells of an immunodeficient patient results in the production of healthy cells. Early results are encouraging, but widespread treatment with gene therapy is years away. Other genetic research is being conducted using stem cells, which are cells taken from umbilical cord blood. When pregnancy screening indicates that a primary immunodeficiency is probable, umbilical cord blood is collected during delivery, the stem cells are taken out and modified genetically, then they are transfused into the child. This technique is also years away from widespread use.

## ***Clotting Factors***

### **Primary Use: Hemophilia**

Typically seen in males, hemophilia is an inherited bleeding disorder caused by a shortage of blood-clotting factors. A person with hemophilia has an excessive risk of bleeding. The two different types of hemophilia are called A and B. Hemophilia A, also called classic hemophilia, is the most common, and it is caused by a deficiency in clotting factor VIII. Hemophilia B is caused by a deficiency in clotting factor IX. An additional bleeding disorder, von Willebrand's disease, is related to the function of platelets, cells that assist with blood clotting.

The treatment of hemophilia requires administration of clotting factors. Historically this was accomplished by blood transfusions, but the amount of clotting factors in a typical transfusion was not enough to treat the bleeding disorder sufficiently. In the 1960s, a concentrated form of factor VIII, also known as cryoprecipitate, was discovered. Administration of cryoprecipitate did not require a blood transfusion, which was beneficial to patients. A few years later, the introduction of freeze-dried forms of factor VIII and factor IX, derived from human blood plasma, allowed hemophilia patients to administer clotting factors at home. Unfortunately, some of these earlier products were contaminated with viruses, so even though hemophilia patients were able to control their bleeding disorder, a few patients were infected with diseases such as HIV or hepatitis. More recent products are recombinant in nature or are highly purified, so the risk of infection essentially has been eliminated. Recombinant factor VIII products include Kogenate® FS, Recombinate™ and ReFacto®, while plasma-derived products include Alphanate®, Humate-P®, Hemofil® M, Monarc-M™ and Monoclate-P®. For factor IX, the only recombinant product is BeneFix®, and common plasma-derived products include AlphaNine® SD and Mononine®. The dosing of clotting factors is highly variable since it is based on patient weight as well as on the severity of disease. All clotting factors are given intravenously, and most patients self-infuse at home.

**Pipeline:** As with several other diseases, the most intriguing research in the field of hemophilia is gene therapy. The gene that causes hemophilia is known, and if this gene were to be modified to become a “normal” gene, hemophilia might be cured. Several gene-therapy products are in clinical trials, including both factor VIII and factor IX products. It will likely be a number of years before these products make it to market. Closer to market are recombinant products that are free of any forms of albumin, which has been linked to impurities (and resulting infections) in the past.