Biotech and specialty pharmaceuticals offer groundbreaking medical advances in the treatment of complex illnesses. These products are high cost, but have made the most profound difference to individuals with conditions such as multiple sclerosis (MS) and rheumatoid arthritis (RA), reducing pain and discomfort, improving quality of life and slowing the progression of disease. With a flourishing pipeline and multiplying indications for products already on the market, the sector is seeing an astonishing growth in utilization. There’s no question that specialty pharmaceuticals are changing standards of care and will play an ever-greater role in our nation’s healthcare in the years to come.

Figure 1

In the 2005 Caremark Book of Business, Specialty/Biotech Spend reached 8 percent.

Source: Caremark Book of Business data
Growth in utilization is the major driver behind specialty’s double-digit trend. Despite significant launches and the approval of additional indications for existing products, Caremark Specialty Pharmacy management programs kept specialty trend to 20.4 percent in 2005—below industry forecasts. Over the year, specialty pharmaceuticals grew from less than 6 percent of our gross Book of Business (BOB) spend to 8 percent—more than a 30-percent increase. Growth in utilization, at 11.4 percent, was consistent with market rates although it was more than twice the overall Caremark BOB rate.
The Specialty Pipeline – New Drugs and Indications Fuel Growth in Utilization

While the specialty segment currently accounts for about 15 percent of pharmaceutical spending in the United States, the specialty pipeline is approaching parity in terms of the number of potential new products. The pipeline is expanding in scope as well as volume. An increasing number of products are aimed at chronic conditions – RA, psoriasis, asthma – with higher incidence rates than the “orphan” diseases that first dominated the specialty sector. For example, three products for macular degeneration are expected to win FDA approval this year, and there are seven additional drugs for the condition in earlier stages of development. More than two million people in the U.S. have wet age-related macular degeneration (AMD), and approximately 200,000 new cases are diagnosed each year. As our population ages, AMD incidence is expected to increase. Products in the pipeline are expected to offer better outcomes than the few treatments currently available.

Figure 3

### Top 10 Specialty Therapeutic Classes

<table>
<thead>
<tr>
<th>Therapeutic Class</th>
<th>Leading Specialty Drugs</th>
<th>Average Annual Cost of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Enbrel, Remicade, Humira, Kineret, Orencia</td>
<td>$15,000 - $20,000</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>Betaseron, Avonex, Rebif, Copaxone</td>
<td>$20,000 - $24,000</td>
</tr>
<tr>
<td>Oncology</td>
<td>Gleevec, Tarceva, Nexavar, Revlimid, Sutent, Iressa</td>
<td>$40,500 - $95,000</td>
</tr>
<tr>
<td>Hematopoietics (used as an adjunct to cancer and other therapies)</td>
<td>Procrit, Epogen, Neupogen, Neulasta, Aranesp</td>
<td>$5,000 - $20,000</td>
</tr>
<tr>
<td>Immunosuppressants (used with organ transplants)</td>
<td>Cyclosporine, Cellcept, Zenapax, ATGAM</td>
<td>$10,000 - $45,000</td>
</tr>
<tr>
<td>Human Growth Hormone</td>
<td>Nutropin, Humatrope, Genotropin, Norditropin, Tov-Tropin</td>
<td>$18,000 - $20,000</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Rebetron, Pegasys, Peg-Intron, Infergen</td>
<td>$24,000 - $30,000</td>
</tr>
<tr>
<td>Infertility</td>
<td>Gonal F, Follistim</td>
<td>$10,000 - $20,000</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Recombinant Blood Factor Products</td>
<td>$150,000 +</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Forteo</td>
<td>$9,000</td>
</tr>
</tbody>
</table>

Ranked by gross cost in the Caremark 2005 Book of Business
This page contains prescription brand name drugs that are trademarks or registered trademarks of pharmaceutical manufacturers that are not affiliated with Caremark.
Also, an increasing number of specialty pipeline products— including oncologics such as the recently approved Sutent (sunitinib malate)— are being developed for oral administration rather than for injection, infusion or inhalation. While oral therapies provide easier administration than specialty injectables, many have complex side effect profiles, or are often used in conjunction with existing therapies, or are used as a first-line therapy before a more intense injectable medication is needed. The complexity of these therapies underscores the need for appropriate management of these individuals through specialty pharmacy services.

Oncologics continue to dominate the pipeline and present some of the most exciting new science. Products such as cancer-preventive vaccines and personalized drugs derived from an individual’s own tumor are likely to have profound effects on cancer treatment.

Much growth in specialty utilization is related to expanding indications for existing products. For example, Humira (adalimumab) was approved in 2002 for the treatment of symptoms associated with moderate to severe RA. Today it has been approved for five additional indications, including the treatment of psoriatic arthritis. Additional indications for Humira are under consideration at the FDA.

Utilization increases may also be related to the expanding promotion of specialty pharmaceuticals, including through direct-to-consumer (DTC) advertising. According to Verispan DTC audits, for example, DTC expenditures for Humira increased more than 80 percent from 2004 to 2005. DTC expenditures doubled for Neulasta, a drug used during chemotherapy to reduce the risk of infection by increasing white blood cells.
Caremark monitors the specialty/biotech pipeline continuously, evaluates the potential impact on utilization and spend and provides utilization management recommendations, where appropriate, for each pending launch. Consult your Caremark account representative for recommendations for appropriate management strategies for pipeline products relative to your plan and plan population.
An Approach to Specialty Management – Better Outcomes, Lower Overall Costs and Appropriate Utilization

A comprehensive CareSolutions approach to specialty management leads to better outcomes, lower overall costs and the assurance that medications are used appropriately. Caremark Specialty Pharmacy management services go far beyond dispensing the medication.

Understanding coverage and cost. Specialty pharmaceuticals may be administered in physician offices or bought at retail pharmacies or through a specialty pharmacy. Some drugs are commonly covered under the medical benefit, others under the pharmacy benefit. Due to all these factors, expenses related to specialty pharmacy costs can be hidden. A review of pharmacy and medical data can often uncover specialty utilization and allow for thoughtful consideration of management strategies.

Proactive pipeline management. Tracking the pipeline to anticipate prospective specialty launches allows proactive implementation of utilization management.

Utilization management. As specialty medications increasingly address more common chronic conditions, utilization management is essential to optimize the plan’s investment and plan participant outcomes. Caremark also offers clients the option to apply clinical guideline management based on clinical practice guidelines and clinical trial literature to help ensure that the right candidates get the appropriate drugs. Once a plan participant is receiving therapy, our guideline management programs can help ensure that appropriate therapeutic endpoints are achieved.

Estimating Specialty Spend: Multiple Sclerosis (MS)

Prevalence stats indicate there will be 895 individuals with MS.

Current treatment data indicate that 554 of those individuals will seek treatment at an average cost of $20,000.

1 Million Population

Plan’s Estimated Annual MS Spend (AWP) $11,080,000

Based on the Caremark prevalence of treatment model, updated January 2006.
Supporting plan participant adherence. Appropriate, consistent use is essential to reap the full benefits of these costly medications, yet the difficulties of self-administration and troublesome side effects can discourage plan participants. Counseling from a health professional with special expertise with these therapies can support adherence. See Figure 7.

Providing extra support. CarePatterns® and Accordant® disease management programs are designed to help individuals understand their chronic conditions and properly use their medications. Through these programs, Caremark addresses a range of chronic conditions by working with patients, caregivers and providers. By combining the strengths of our Specialty Pharmacy services with disease management principles, Caremark offers an integrated delivery model that further enhances outcomes and decreases overall healthcare costs.

Caremark Specialty Pharmacy Provides More than Medication for Plan Participants

• Specialty drug fulfillment
• Convenient delivery
• Adherence management
• Proactive refill reminders
• 24/7 clinical support
• Care coordination
• Extensive education and counseling
• Self-injection training

Figure 7

Adherence to Care – Encouraging appropriate drug regimen adherence.

Source: Caremark Analytics and Outcomes analysis, 2005
Adherence – Plan Participant-Level Compliance + Plan Participant-Level Persistency. Compliance – How well a patient follows the physician’s orders with a prescribed therapy regimen. Persistency – The duration that a patient follows the therapy regimen.
HEPC: hepatitis C; HGH: human growth hormone; MS: multiple sclerosis; RA: rheumatoid arthritis.
The Ongoing Challenges of Specialty Pharmacy Management

This year marked a major milestone in the specialty pharmaceutical market. In late May, the FDA granted approval to a bio-generic – Omnitrope, a human growth hormone product similar to Genotropin. While this is an encouraging development, it must be noted that human growth hormone products are among the few biologically derived drugs that are approved as chemicals rather than biologics. Furthermore, the FDA did not rate the generic product as equivalent to and freely substitutable for the brand.

Although patents for several biologically-derived pharmaceuticals have expired, or will expire soon, there is still no clear regulatory pathway that allows an abbreviated approval process for most bio-generics. Bio-generics present distinct approval challenges. More traditional “small molecule” drugs are typically combinations of chemicals. Biotech products are often large protein molecules derived from living cells – a much more complex manufacturing process. There are concerns that deviations from the current standard processes for specific biotech products will affect safety and efficacy. It is up to the generics manufacturer to demonstrate bioequivalence for potential bio-generic products. In turn, these demonstrations must be affordable to incent the manufacturer.

Market forces – notably increasing specialty utilization and the shift to public funding for a significant portion of our national pharmaceutical expenditure due to Medicare Part D – may come together to speed the development of a broader bio-generic approval pathway. With the expectation that such legislation will be enacted, some generics manufacturers are preparing to develop more bio-generic products for U.S. distribution.

As more specialty and biotech medications are introduced, plans may consider whether they could benefit from implementing traditional pharmacy benefit management strategies such as formularies to help control costs. However, the very differences that distinguish specialty pharmaceuticals from more traditional brand name products can make such a strategy problematic. Many specialty products act on a cellular level. Even within a therapeutic category, response can vary widely from person to person, as well as in a single individual over time. The complexity of the conditions being treated also complicates choice of therapies, increasing the need for careful one-on-one management of the plan participant. For all of these reasons, there are more limited opportunities for therapeutic interchange in specialty pharmaceuticals at the present time. Your Caremark account representative can work with you to explore specialty management strategies appropriate for your benefit plan and population.

IMS calculates that eight major molecules with global sales of $15 billion could potentially go generic by 2010.