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Drugs in the
Development
Pipeline:
Impact on Part B
Medicare Spending

*A study conducted by NORC at the University
of Chicago and Georgetown University for the
Medicare Payment Advisory Commission*

**Drugs in the Development Pipeline:
Impact on Part B Medicare Spending**

Submitted to the Medicare Payment Advisory Commission

by

NORC at the University of Chicago

and

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Summary

Coverage of pharmaceutical products under Medicare Part B is extremely limited. Nevertheless, expenditures by Medicare for outpatient drugs, in 2001, were approximately \$6.4 billion and rising at a rate of over 20% per year over the past three years. This report characterizes pharmaceuticals in the process of development that are likely to affect Part B expenditures. It includes a list of pharmaceuticals currently in development, as well as a synthesis of information regarding pipeline drugs and trends obtained from interviews with selected experts.

The list compiled for this project contains over 650 drugs and biologicals in development by over 100 pharmaceutical and biotechnology companies. While the list provides important insights into the trends related to pharmaceutical development, it is not an exhaustive or definitive compilation of pharmaceutical agents.

Nearly one fourth of the drugs on the list are in the late stages of development (Phase II/III or later). Some drugs are currently on the market for one or more indications, but are being investigated for treatment of other conditions. About 70 percent of the drugs on the list are indicated for the treatment of various cancers, although treatments for cardiovascular disease, hemophilia, multiple sclerosis, HIV, arthritis, dermatological conditions, and Crohn's disease are also represented. Of those not indicated for the treatment of cancer, about 50 are indicated for the treatment of cardiovascular disease.

The list of pharmaceuticals contains information on mode of administration for each pharmaceutical wherever possible. About 40 percent of the drugs included in the list are estimated to be eligible for Medicare Part B coverage based on non-self administration. Approximately 10 percent are estimated to be ineligible for coverage because, while injectible, the administration is subcutaneous. No information on mode of administration was available for about half the pharmaceuticals on the list. Because of how the list was compiled, many are likely to be administered by a physician, and others are thought to be substitutes to existing cancer treatments currently covered under Part B.

Information from interviews with pharmaceutical industry experts, combined with insights provided by the list of pharmaceuticals, helps illustrate some important trends that are likely to affect Medicare Part B spending.

- A large number of biological agents are in the development process. Several important characteristics of biological agents distinguish them from chemical agents, including their wide range of therapeutic relevance, mode of administration (injection or infusion, at least in initial stages), relatively lengthy FDA approval process, and the absence of a process for approving generic equivalents.
- While a large number of treatments for cancer are in the pipeline, some respondents suggest that the market for drugs that treat a single cancer diagnosis is diminishing for both economic and scientific reasons – particularly given the low prevalence of many cancers. On the other hand, there have been important innovations in new types of cancer treatments that target a particular step in the process of tumor development and which are likely to be used in conjunction with existing treatments.

- Informants suggest there is also a trend toward development of physician-administered pharmaceuticals for new indications. These include agents in relatively new classes, such as disease-modifying anti-rheumatic drugs (DMARDs), interleukins, and monoclonal antibodies. For various reasons (e.g., the size of the molecule), they are more likely to involve physician administration at least at first. Some of these drugs are important for future Part B spending because they treat conditions with high prevalence in the elderly, such as heart disease, rheumatoid arthritis, and diabetes.
- A trend to new forms of self-administered drugs may temper the expansion of drugs eligible for coverage under Part B. Experts note that there is a significant trend by manufacturers toward the development of self-administered agents (oral, inhalable, or transdermal) over existing injectibles.

Overall, a number of complex and interrelated factors characterize the landscape of pharmaceuticals in the pipeline and their likely impact on Medicare Part B spending. Some potential slowing of the development of new cancer therapies may be offset by new physician-administered treatments for other (more prevalent) clinical indications. And while development of biological agents may tend to move treatments into the physician's office, manufacturers are quickly seeking to develop more convenient formulations of many drugs that allow self-administration. The long term effect of these factors is difficult to predict.

Introduction

The Medicare Payment Advisory Commission (MedPAC) engaged the team of NORC at the University of Chicago and Georgetown University to characterize developmental drugs and biologicals of particular interest to policymakers under current Medicare Part B coverage rules. The deliverables under this project include the attached list of drugs and biologicals, as well as this memo, which describes the methodology used and summarizes key findings and trends. The memo is organized around the following topics:

1. Overview and context. We begin our discussion with a brief overview of Medicare rules for coverage of drugs and biologicals in outpatient settings, as context for the specific discussion of our research findings.
2. Project methodology. We describe project methods and implementation. Given the short turn-around nature of the project, we rapidly searched sources of readily available public information on drugs and biologicals in development and conducted several brief telephone interviews with key informants.
3. Database of pipeline drugs. We describe in detail our list of over 650 Part B-relevant drugs and biologicals under development and provide summary statistics describing the content of the list.
4. Trends in pipeline drugs. We discuss what we have learned about general trends in new drugs in the development pipeline, particularly those that may be reimbursable under Medicare's rules for Part B. This discussion is largely drawn from our interviews with key informants.
5. Case studies. In this section we describe selected examples of pipeline or recently approved Part B-relevant drugs and biologicals. These scenarios are based on individual entries in our database. While they are not representative of all scenarios that might occur, we think these cases illustrate some of the findings of our project as much as the aggregate results.

Although time limitations for this project precluded the creation of a comprehensive list of all Part B-relevant drugs and biologicals in development and definitive determinations of all data elements relevant to questions of interest to MedPAC, we believe that the attached list and accompanying analysis should be helpful to MedPAC.

Overview and Context

Coverage of pharmaceutical products under Medicare Part B is extremely limited. In general, drugs and biologicals are covered if they typically require physician administration, constitute an oral substitute for a covered injectable or infusible treatment for cancer, or are a complement to a covered treatment (e.g., drugs treating anemia resulting from chemotherapy). Drugs may also be covered if they are attendant to use of durable medical equipment (DME) or if they belong to a set of specified, self administered drugs and biologicals, such as blood clotting factors. In September 2001, the General Accounting Officer reported coverage for approximately 450 distinct drugs and biologicals under Medicare Part B coverage rules.¹ At its March meeting, MedPAC reported that Medicare spent approximately \$6.4 billion for outpatient drugs in 2001, a figure that has been increasing at a rate greater than 20 percent per year over the last three years.²

The current project is of particular interest to MedPAC and Congress because rapid advances in drug development lead to frequent shifts in the number and type of drugs that constitute the core of Medicare Part B expenditures. As part of the study cited above, the GAO found that approximately

75 percent of Medicare Part B spending on drugs and biologicals in 1999 was associated with 20 of the approximately 450 covered drugs and biologicals.

Drugs and biologicals that have implications for Part B Medicare spending are rapidly evolving. Medicare Part B rules accommodate coverage of a large number of drugs and biologicals used in the treatment of cancers, as well as therapies that fall into the category of biologicals such as monoclonal antibodies, gene therapies, cellular therapies and protein therapies. Biological therapies today are almost exclusively administered via injection or infusion and are thus particularly relevant for Part B coverage. Because so many of the drugs and biologicals involved in cancer treatment fall into this category or are covered under Part B for other reasons, all drugs with an indication of cancer are of potential interest to Medicare.

In addition to cancer and other indications for which a large number of treatments are not self-administered, Medicare drug spending may also be affected by innovative treatments for conditions with a relatively high prevalence in the elderly population. This includes the development of new biologicals for the treatment of asthma and rheumatoid arthritis. We have attempted to address this interest by paying particular attention to potential candidates for Part B coverage in development with indications such as heart disease, arthritis, and other conditions highly prevalent in the over 65 population. Our findings in this area are summarized in both the trends and case studies sections below.

Project Methods

As described above, there are two main components to our work for the current project:

- the review and summary of available information on the Part B-relevant drugs in the development pipeline and
- targeted, brief telephone interviews with key informants knowledgeable about the drug development pipeline.

Our process closely followed the summary of methods described in the one-page statement of work that accompanied our task order proposal dated February 19, 2003, and reflects efforts beginning in advance of and following the official project kick-off meeting conducted at MedPAC's office on March 4, 2003. In the paragraphs below we provide details on our activities under both of these broadly defined tasks.

Search strategy. Consistent with current Part B coverage rules, we targeted search activities around information on drugs that are physician administered, attendant to DME use, and direct substitutes for physician-administered drugs. In addition, because the current rules accommodate substantial coverage of cancer therapeutics, we gathered information on all new cancer medications. Finally, we also attempted to capture all information representing development of drugs classified as biologicals.

Our sources of information reflect the short turn-around nature of the project. Specifically, we targeted peer-reviewed literature, industry trade newsletters, online information published by the federal government, trade associations and pharmaceutical benefit managers (PBMs), and relevant Wall Street analyst reports. Almost all sources were identified electronically, either through the Internet or through the University of Chicago's subscription to multiple Dialog™ databases. We also reviewed hard copy materials from industry trade newsletters acquired through the National Library of Medicine (NLM) in Bethesda, MD. The comprehensive list of sources referred to for this project follows:

- Online publications: Government websites: fda.gov, cms.gov, MedPAC.gov, nci.nih.gov
Foundation websites: kff.org, rwjf.org; association and industry websites: PhRMA.org, Merck-Medco, Express Scripts, Advanced PCS; Other Internet searches: google.com, altavista.com, biospace.com, dresources.com, pdr.net, <http://www.biospace.com/cciss>, and <http://www.centerwatch.com/patient/cwpipeline>.
- Information searched via Dialog™: industry trade newsletters: The Pink Sheet, Scrips, Centerwatch, Drug Cost Management; Atlantic Information Services newsletters; Wall Street Analyst reports from Raymond James International, Lehman Brothers, Data Monitor, Inc., Technology Catalyst International, IMS Health and other investment banks and Wall Street firms specializing in pharmaceutical industry analysis.
- Peer-reviewed publications: conducted a comprehensive search of NLM's Medline™ database on the key words described below.

Secondary sources used for the preparation of this memo are cited as end notes. A comprehensive set of sources used in compiling the database is provided as an appendix to this document. In the case of electronically available information from Dialog™ and Medline™, we conducted searches on a series of key words. For information gathered in hard copy from the NLM holding we conducted a manual search on the same key words.

List compilation. In compiling the attached list we attempted to maximize both accuracy and comprehensiveness while producing data of use to MedPAC. Through the sources listed above, we were able to identify information regarding names of products in development (chemical, product, or generic names), the sponsoring pharmaceutical company, and the indications for which the drug is undergoing trial. In almost all cases we were able to obtain information regarding the specific developmental phase, and in many cases information on mode of administration. Wherever possible we verified the developmental phase using multiple sources because there is substantial attrition at each phase of the R&D process and because there were modest differences in the time of publication of the various sources we consulted. There was substantial overlap in lists obtained over the Internet, particularly lists from recent PhRMA surveys, from PBM websites and newsletters.

A major barrier encountered in this exercise was the lack of information on mode of delivery for developmental drugs, an important factor in determining Part B coverage. This was a particular concern for drugs in Phase III of development as these are the ones most likely to affect Medicare expenditures in the relative short term. In order to supplement this information, we used our team's clinical expertise to make educated determinations of mode of administration and hence Part B coverage status. As these determinations were made primarily to help MedPAC anticipate new agents that would be eligible for coverage over the next 5 to 10 years, we did not go through the same process for Phase I and Phase II drugs. We note that this information can be verified more systematically using proprietary databases or by obtaining more time of clinical experts, but this would require time and expense beyond our existing contract.

Conduct of key informant interviews. In coordination with MedPAC, we identified and contacted several individuals for participation in brief interviews exploring issues related to Part B-relevant drugs in development. The goal stated in our task order agreement was to conduct interviews with at least three individuals, focusing on the following themes:

- Trends in the development of drugs and biologicals as they relate to the current Part B coverage rules, particularly their assessment of the potential growth in the number of provider-administered drugs relative to self-administered drugs over the next 5 to 10 years.
- Trends in developmental or recently approved drugs, classes of drugs or biologicals that are provider administered and have potentially high utilization among the Medicare beneficiary population.
- Trends in the development of different modes of administration for drugs and the resulting effects on the possibility of Medicare Part B coverage.

We found it surprisingly difficult to obtain useful interviews. Several people identified as knowledgeable told us they could offer only limited insights, while others declined to help us because of concerns about nondisclosure agreements with their clients in the industry or unwillingness to provide uncompensated advice. In the end we collected some useful insights from respondents including representatives from an investment research firm, a pharmacy benefit manager (PBM), two industry trade organizations, a pharmacy school, and the Institute of Medicine.

Database of Pipeline Drugs

In going through the process described above, we have identified over 650 Part B relevant drugs or biologicals that are going through the Food and Drug Administration's (FDA) clinical trial process or that have recently submitted new drug applications (NDAs) or product license applications (PLAs) to the FDA.³ The majority of these are new drugs, not yet approved for marketing or dissemination, that comprise the pool from which drugs that represent substantial Part B drug and biologicals spending over the next decade will emerge. A limited number of entries in our database are drugs that are already approved by the FDA for marketing and dissemination under specific indications. These drugs are still listed on recent publications of drugs in development and may represent covered therapies whose utilization will increase in the coming years with increased education on the part of clinicians. Although approval under a specific indication does not by virtue of FDA regulation or Medicare rules preclude use and reimbursement for other indications, we include these drugs because approval under a new indication may increase their utilization and the cost they represent for Medicare. Before describing the list in greater detail, we offer some important notes regarding interpretation of the information in the database.

Fields. As described under in the methods section above, we attempted to provide MedPAC with fields appropriate for the purposes of anticipating new Part B relevant drugs and biologicals. Our database includes the following fields:

- Product name: this category includes available information about the product name, generic name, and other characteristics such as chemical composition. The product name and generic name are separated by a '/'. In some cases, only a product name was available, whereas in other cases only a generic name was available.
- Development sponsor: we include information on the pharmaceutical industry sponsor of the development and clinical trials for each entry. Several entries have more than one sponsor. In one or two cases, no sponsor information was available.
- Relevant indications: we provide names of clinical indications for which the drugs are currently undergoing trials. The majority of drug entries are in development for multiple indications. As

noted previously, there are some drugs on the list for which approval for one or more indications has already been established.

- Developmental phase: wherever possible we specify the phase of development for each entry as Phase I (safety trials), Phase II (efficacy trials) and Phase III (clinical efficacy relative to existing therapy). If a drug is in development for a range of indications, multiple phases are listed.
- Part B coverage: as described above, information regarding mode of administration for each drug was not always available. In these cases we made baseline determinations of Part B coverage status using the team's clinical expertise. Because this determination was less than scientific, we focused only on Phase III drugs for this portion of the exercise. We also made efforts to determine the mode of administration by relying on a variety of Internet resources, such as the on-line PDR, Medline, PubMed, and drug manufacturer websites. The following codes were used to ascribe the logic for our assessment of coverage under Part B. Where there was insufficient information available, the cell is entered as 'unknown'.

covered (1) = likely to be covered because non-self administered, outpatient

covered (2) = likely to be covered because vaccine

not covered (1) = not likely to be covered because mode of delivery is oral, nasal, or topical

not covered (2) = not likely to be covered because mode of delivery is subcutaneous (self administered) injection

not covered (3) = not likely to be covered because inpatient drug

- Source(s): a brief citation of the source of the drug is provided. A complete list of drug sources is included as an appendix.

Limitations of the database. Although we have made our best efforts to conduct the project in strict adherence to the process presented in our original proposal, we note that the limited timeline and resources for this project precluded completion of a complete list of Part B-relevant drugs and biologicals in development. There are considerable differences among estimates of the total number of drugs in development by specific category or indication. One reason for these discrepancies is that new products are constantly entering and exiting the development process. Furthermore, the data available in the consulted sources are not sufficient in many cases for determining whether Part B coverage is likely. These caveats aside, we believe that the list presented here is representative of the larger universe of new drugs and biologicals in development that are candidates for Medicare Part B coverage under existing rules.

We believe that the individual entries in the database are as accurate as possible within the limitations discussed. As noted above, however, mode of administration and Part B coverage status often are not available in the sources we consulted. We have used clinical expertise to provide this information as accurately as possible. But we do not represent this list as accurate for each individual drug with regard to this imputed information. We do believe, however, that it is valuable for purposes of identifying broad trends.

Summary of findings. As described above, we have identified over 650 specific drugs and biologicals that are in development, recently approved or awaiting response to pending final approval from the FDA. Sponsors for these drugs include over 100 distinct pharmaceutical and biotechnology companies and the National Cancer Institute. Approximately 10 percent (67 products) of the products identified are currently on the market. These include products currently in trials for new indications and products that have recently received approval from the FDA.

Developmental products listed in the database target a variety of indications, including the traditional Part B-relevant indications such as cancer (approximately 436 identified), hemophilia and multiple sclerosis. The database also includes drugs for several other indications with implications for the Medicare population such as HIV (approximately 25 identified), arthritis (approximately 15 identified), dermatological conditions (approximately 8 identified), and Crohn's disease (approximately 10 identified). It is important to note that the many of the products target multiple conditions. The bullets below summarize additional characteristics of the drugs we found. Because of the limitations of time and the search strategy discussed above, these statistics are not likely to be representative of the universe of drugs in the R&D pipeline.

- We estimate that 42 percent of the products included in our list are non-self-administered (i.e., intravenous or intramuscular injections) and therefore likely to be covered by Medicare Part B. Of the remaining products we do not have information relevant to coverage for 55 percent of them and approximately 11 percent of them are likely not to be covered by virtue of being subcutaneous injectables. The majority of the products that are “not covered” under current rules represent new cancer therapeutics of potential interest to MedPAC since they could be substitutes for covered cancer therapies.
- Approximately 22 percent of products identified are in late stages of development (Phase II/III and beyond) and, if successful, are likely to be marketable in the next five years.
- Products primarily indicated for cancer make up over 70 percent of the overall list and approximately 60 percent of late phase products listed.
- Of the approximately 30 percent of drugs not indicated for cancer, about 55 agents have a primary indication of cardiovascular disease. Of these, 8 are in late phases and are likely to be covered (if approved) under Part B. Among products for other non-cancer indications there are a smaller number of late-phase products potentially eligible for Part B coverage (e.g., 4 HIV/AIDS products).
- A substantial majority of the products for which we are unable to make a determination relative to Part B coverage are still in Phase I or II. They are included in the database either because they are for a cancer indication, or because they are biologicals likely to be injectable.
- While it is difficult to predict the impact of these products on the scope of overall Part B spending on drugs and biologicals, there are significant numbers of biologicals and, in particular, therapeutic vaccines (over 50 identified), interleukins/interferons (over 20 identified), and monoclonal antibodies (approximately 36 identified) in the R&D pipeline.

Trends in Pipeline Drugs

A listing of drugs in the development pipeline, while useful, only tells one part of the story. We conducted interviews with several key informants with the purpose of identifying broader trends that might be missed in focusing on individual drugs.

The development pipeline is slow and unpredictable. Many of the drugs and biologicals in development, particular in the early stages will never make it to market. The FDA's earliest clinical trial phases are designed to produce results related to safety (Phase I) and baseline efficacy of (Phase

II) of candidate compounds. Recent estimates indicate that only one in 10,000 to 15,000 compounds undergoing laboratory screening make it to the U.S. market as approved pharmaceuticals. Of the drugs making it through pre-clinical phases to Phase I of the FDA approval process only about 20 percent eventually gain FDA approval, while 40 percent of drugs in phase II and 50 to 80 percent of drugs in phase III gain approval for marketing.⁴ These figures are attributable in part to the failure of compounds being tested to demonstrate to the satisfaction of the FDA the safety, efficacy or relative effectiveness compared to existing therapy for the specified indication. In addition, for approximately seven percent of drugs that make it through to Phase II trials, the trial sponsor discontinues development for commercial reasons. Given these estimates, we may infer that fewer than half the drugs on our list will go to market.

Another variable to consider when assessing the status of drugs in the development pipeline is the time to market for successful compounds that are currently at various phases of the development process. The Tufts Center for the Study of Drug Development estimates that the process of drug development from the earliest phases of research through FDA trials and approval lasts, on average, 10 to 15 years.⁵ The pace of development and the rate of attrition emphasize the relevance of drugs and biologicals in later phases of the trials process (especially Phase III) as those that are most likely to affect Medicare's Part B drug spending over the next several years.

Development of biological drugs follows a different pattern than chemical compounds. Biological drugs are organic compounds with therapeutic implications for a wide range of chronic and acute conditions affecting Medicare beneficiaries. The majority of the drugs identified in our database are biological drugs and, by some estimates, the total number of biological drugs in development exceeds 800. This category of therapeutics broadly includes gene therapies, human cell therapies, monoclonal antibodies, interferons, interleukins, colony stimulating factors, and therapeutic vaccines. Perhaps the defining characteristic of biological drugs as they relate to Medicare Part B is their flexibility as therapeutic agents. Because many are identical in design and function to naturally occurring proteins or cells, the range of potentially relevant indications for each agent is quite broad. Interleukins are examples of biologic agents that look promising for a range of diagnoses, including rheumatoid arthritis, asthma, multiple sclerosis, and HIV treatment. According to some estimates, for HIV related conditions alone, chemokine modulators (a subcategory within interleukins) are expected to generate \$1-2 billion in sales by 2012.

A recently released study conducted by S.G. Cowen Securities estimates 11 percent annual growth in the size of the overall market for biological drugs over the next three years, culminating in a total market of \$55 billion by the year 2006.⁶ The same report estimates that the market for monoclonal antibodies, a subset of biologicals, will grow 15.6 percent between 2001 and 2006.⁷ Cowen's analysis of the "top ten" biological products in terms of potential revenue, includes at least two Part B coverage relevant therapeutics – Antegren, described in greater detail below, and Avastin, a cancer-related biological.

The Biotechnology Industry Organization (BIO) estimates that about 350 biologicals are in the late stages of development. Due to greater complexity in both the development process and the FDA approval process, even late-stage biotech drugs may take over five years to get to market. Because of how biotech drugs are made, FDA must review all manufacturing steps. For example, the scaling up of manufacturing from small quantities for experimentation to large quantities for market is difficult for the companies and requires further review. While there are currently no generic equivalents to innovator biologicals on the market, a number of companies have biogenerics in their pipeline. The FDA is in the process of developing guidelines for establishing approval of generic equivalents to brand name biological agents.

Most new biological drugs require administration in a non-oral form. Yet, while many are administered by injection, the industry suggests that the future may include inhaled formulations or products that are switched on by radiation. In the short term, most biotech products will probably fall under Part B coverage criteria. But over the long term, more of these products can likely be self-administered, such as through the use of small inhalers (not requiring the purchase of durable medical equipment). Others, such as radiopharmaceuticals, will be provided in hospital settings today, but could move to the physician's office in the future.

As part of a 2002 survey of drugs in development, PhRMA has identified 371 drugs in development in the category of biologicals. These products are largely characterized in our list. While the majority of these fall into the category of cancer therapeutics that target the body's immune system to either eliminate cancer or treat the effects of other cancer therapies, over one-third of these drugs are relevant for indications other than cancer. Of particular relevance to future Medicare Part B spending, there are some biological drugs in development targeting cardiovascular conditions such as congestive heart failure. Biologicals in this category include Natrecor/nasiritide (highlighted below in the case studies section), toborinone, immune modulation therapy (being developed by Vasogen), Angiogenix, YM-087, and Conivaptan (receptor antagonist).

The pipeline contains many new cancer therapies, yet development of new cancer drugs may have slowed somewhat for both economic and scientific reasons. As currently constituted, drug and biologic treatments for cancer are more often covered than products for other indications. This is primarily because of the complexity of cancer therapy and the need for use of non-self-administered pharmaceutical and biologic products both as stand-alone therapy and in conjunction with other therapies, in particular, radiotherapy. Furthermore, the addition of direct substitutes for non-self-administered agents to the category of products covered under Medicare Part B has increased the number of cancer medications eligible for coverage. And there has been some consideration of extending Medicare coverage to all cancer drugs and biologicals, rather than excluding the limited number of products that do not fit the current requirements.

One of our key informants suggested that the number of new cancer drugs approved is down, in part because the market for a drug that treats a single cancer diagnosis is small outside the four largest varieties (breast, prostate, lung, and colorectal). Furthermore, modern science is subdividing many types of cancer, and many new drugs do not work across these smaller subcategories. A good example is Gleevec, the new oral drug used to treat very specific forms of leukemia.

At the same time, some new advances may increase the number of new cancer drugs in the pipeline. One key informant pointed out important areas of innovation in cancer therapy, specifically involving drugs that, like Gleevec, target a precise step or factor involved in tumor growth or spread. Drugs like Avastin (an investigational monoclonal antibody with potential use in breast, colorectal, and some lung cancers) and Erbitux (another monoclonal antibody that is being tested for use in colorectal and other cancers) are examples of these newer drugs. The potential of these types of drugs is significant, because the therapies tend to be used in combination with other therapies, at least initially, and may not replace existing drug use.

What is hard to predict is the balance between the forces that may slow the emergence of new cancer therapies and the new areas of innovation.

The pipeline includes some significant new therapies for conditions other than cancer, including a strong trend toward approvals for new indications in some classes of drugs. An important finding from the current exercise is the growth in development for Part B relevant drugs and biologicals affecting conditions other than cancer. Of the products identified in our database, about 30 percent are for non-cancer indications. Furthermore, of those products identified that are primarily related to a diagnosis of cancer, many are potentially relevant for non-cancer indications as well. As described

above, key non-cancer indications that may be affected by the products included in our list include cardiovascular disease, hemophilia, multiple sclerosis, Crohn's disease, HIV/AIDS, asthma, and a number of dermatological conditions. Because the pharmaceutical market for these drugs is dominated by oral medications, new products in the injectable category must represent new mechanisms of action with substantial benefits over existing therapies.

Several examples of drugs recently approved or in late stages of development are included in the case studies in the last section of this report. Some categories that were emphasized by our key informants include:⁸

- Disease-modifying anti-rheumatic drugs (DMARDs). One informant told us about substantial new developments in this group of drugs that is used to treat rheumatoid arthritis as well as autoimmune ailments such as lupus, psoriasis, and Crohn's disease. DMARDs include tumor necrosis factor (TNF) inhibitors. Although the TNF was first studied in the context of cancer, it has been implicated in other diseases such as rheumatoid arthritis, Crohn's disease, and psoriasis, and the potential exists for their use in many other disease states. Developments here include finding new indications (e.g., lupus) for currently approved drugs like Remicade. The potential here for treatments for conditions that are poorly treated today suggests the potential for rapid expansion of their use.
- Interleukins. Described briefly in the section on biologicals, interleukins were labeled by one key informant as a "sleeper category." Although some interleukins are used for cancer treatment, they are increasingly being studied as treatment for other diseases such as asthma, multiple sclerosis, or lupus.
- Monoclonal antibodies. This category provides a different mechanism for action than many currently available therapies. Antegren, a treatment under development for multiple sclerosis and described in the case studies, belongs to this category.

The potential represented by new drug therapies for conditions other than cancer is illustrated by data on the prevalence of major chronic conditions (see Table II). While cancer affects many Medicare-eligible Americans, the prevalence of heart disease, hypertension, and arthritis in the senior population is greater.

Table II. Prevalence Estimates: Major Chronic Conditions for Americans Over 70 (% of population over 70)

	Male	Female
Stroke	10.4	7.9
Diabetes	12.9	11.5
Cancer	23.4	16.7
Heart Disease	24.7	19.2
Hypertension	40.5	48.0
Arthritis	49.5	63.8

Source: CDC, National Center for Health Statistics. Supplement on Aging Study and Second Supplement on Aging Study, 1995.

Some new therapies, especially for cancer, will substitute for existing therapies while others will add to the therapeutic arsenal. Treatments for cancer and other conditions may be combinations of therapy including surgery, chemotherapy, radiation therapy, and biological therapy. Often some therapeutic approaches are indicated for combating the physiological processes at the root of the condition while others act to alleviate serious symptoms associated with the condition or the primary therapeutic strategy. For the products in our database, some will simply replace existing therapies or elements of combination therapies and others will be new therapies that add to existing combinations of therapy. Further investigation of this distinction, beyond the scope of the current project, may be warranted to make better use of the information provided in the database.

Many new cancer treatments are substitutions for drugs that are currently reimbursed under Part B, as one form of chemotherapy replaces another. New therapies for other conditions, even if they substitute for existing oral drug therapies, may be new to the Part B coverage category.

A trend to new forms of self-administered drugs may temper the expansion of drugs eligible for coverage under Part B. Although the number of products in the database suggests a potential increase in the number of drugs and biologicals covered under Part B, this increase may be mitigated by other market factors. Several key informants indicated that, despite the incentives created by Medicare Part B coverage rules, there is a strong movement in the industry to develop oral, inhalable, transdermal, or other self-administered formulations. Even in cancer treatment, one informant told us that increased use of oral cancer drugs was already having an effect on the use of infusion therapies.

Several companies are working on inhalable formulations of therapies ranging from insulin and human growth hormones to drugs for multiple sclerosis and hepatitis. These formulations are designed for use with a small inhaler, not a nebulizer or other type of DME. An inhalable formulation for drugs to treat COPD might be available in the next 5 to 10 years. Other companies are developing transdermal formulations, especially for pain management. Anti-seizure drugs and morphine may be administered through a patch over the next few years. There are also new developments in implantable pumps or topical treatments.

The incentives created by Medicare coverage rules to develop physician-administered forms of drugs are countered by other market incentives. Unquestionably, Medicare coverage rules create an incentive for some companies to focus on development of physician-administered drugs that will qualify for Medicare payment. But several key informants emphasized that there is a strong market factors that counteract those trends. For smaller companies that are focused on development of a single product, it is far more important to get the product to market than to worry about the advantage of a particular formulation relative to payment. In the biotech segment of the industry, only ten percent of companies actually have a product on market at present. Patients look at the convenience of self-administered drugs, and physicians may see the likelihood of better compliance. Furthermore, it is important to remember that for many conditions, the majority of patients are covered by private insurance, not by Medicare. Several of the key informants believed that on balance the trend towards self-administration currently exerts a stronger influence on R&D decisions than does potential Medicare coverage.

For some conditions, there may be shifts from hospital settings to the physician's office that parallel the movement of other drugs to self-administration. Even at the same time that some treatments are moving from physician-administered drugs to therapies that can be self administered, some other treatments may move from hospital inpatient or outpatient settings to the physician's office. We were told by one informant that some biologicals require close monitoring at first, but once the doctors has seen the patient's reaction, future treatments can move to the office.

Conclusion: It is difficult to judge the relative magnitude of various trends that may move the volume of Part B drug utilization in different directions. We asked several of the key informants to comment on the relative magnitude of some of the different trends we discussed, but we heard no consistent answer. Some informants suggested the potential for a spike in Part B drug use for the next several years as some of the drugs and biologicals – especially those for non-cancer conditions – come to market. But they speculated that the significant shift to oral and inhalable formulations might flatten or even reverse the upward trend. Others thought that the development pipeline, especially new advances in biotechnology and pharmacogenomics, could keep the trend line heading upward, even while some therapies are shifted to self-administration.

Case Studies

Recent developments in the pharmaceutical sector offer some insights into the pipeline for new drugs and, consequently, have implications for Medicare expenditures under Part B. Some drugs that are either in the pipeline or have recently received FDA approval are illustrations of new types of treatments for conditions where no new drugs have been approved in a number of years. In the case studies below, we highlight several promising new therapies of potential relevance to Medicare Part B spending.

Natrecor (generic name = nesiritide). The drug, Natrecor, generic name nesiritide, is an illustration of a recently approved drug for a condition where no novel drugs have been introduced in over 10 years.⁹ It also highlights the industry's active interest in promoting research into this new form of therapy.

The FDA approved Natrecor in August 2001 for the treatment of congestive heart failure (CHF). CHF affects a large proportion of the population, particularly those 65 and older. The prevalence of CHF for people age 60 through 69 is five percent and the prevalence for individuals 70 and older is ten percent. Rates increase significantly with comorbid conditions such as hypertension.¹⁰ Congestive heart failure is responsible for the majority of hospitalizations in the United States for patients over 65.¹¹

Scios, the company that developed the drug, has historically focused on the development of treatments for cardiovascular and inflammatory diseases. Before Natrecor, the standard treatment for CHF involved the use of inotropic drugs, which boost heart muscle contractions and increase blood flow, and nitroglycerin. Use of these drugs, however, is related to increased mortality despite their effectiveness in improving blood flow. Nesiritide, an injectable drug, is a bioengineered version of hormone naturally produced by the body in response to congestive heart failure. In clinical trials, nesiritide in conjunction with standard therapy performed significantly better in terms of relevant outcome indicators than standard therapy and inotropic drugs.

Resulting directly from the successful development of Natrecor by Scios, Johnson & Johnson recently announced that it would purchase Scios for \$2.4 billion net of cash. A statement by the worldwide chairman for Pharmaceuticals Group, J&J clearly noted that Natrecor was behind the acquisition saying, "Natrecor is a unique product for a largely underserved and growing market. Scios also brings an advanced research program on kinase inhibitors, which is an exciting new area of research."

Xolair (generic name = omalizumab). Xolair is an illustration of research into a new type of treatment for a condition where several accepted treatments already exist. In clinical trials sponsored by Genetech, Novartis, and Tanox, subcutaneous injection of omalizumab is showing promising results for both asthma and allergic rhinitis, as well as for other conditions. Xolair, a monoclonal antibody, differs substantially from existing treatments. Monoclonal antibodies work by targeting the mediators of the immunopathogenic response, such as immunoglobulin E. These antibodies are

responsible for producing the manifestations of the pathophysiologic response, such as wheezing, in asthma. For asthma, Xolair could be an improvement because it can either reduce or eliminate the use of steroid medication. This is an important development in the treatment of asthma, not only because of improved quality of life days, but also in terms of mitigating some of the long-term negative effects associated with oral corticosteroid use. Development of pharmaceuticals such as omalizumab is important for Medicare B drug expenditures because of the relatively high incidence of the disease in the elderly population. The prevalence of asthma in the elderly population in 1996 was approximately 4.6 percent. Asthma prevalence tends to be higher for females than males, and for blacks and Hispanics than whites.¹²

Xolair, and monoclonal antibodies in general, are a promising new treatment for a variety of conditions. Because of their potential usefulness in several disease markets, monoclonal antibody agents are expected to have an important impact on the pharmaceutical industry in upcoming years

Remicade (generic name = infliximab). Remicade, generic name infliximab, is another illustration of the growing importance of monoclonal antibody agents in pharmaceutical research. Manufactured by Johnson & Johnson, Remicade is a monoclonal antibody that works by blocking the activity of tissue necrosis factor alpha (TNF-alpha). TNF is a key inflammatory mediator whose overproduction leads to the inflammation seen in a variety of immune mediated inflammatory disorders. Following successful clinical trials in 1998, Remicade was the first biologic agent indicated for the treatment of Crohn's disease. In combination with methotrexate, Remicade was also the first drug approved by the FDA to improve physical function of patients with moderate to severe rheumatoid arthritis who do not respond to methotrexate alone.¹³ Since the success of Remicade, two other TNF alpha drugs (Humira and Enbrel) have been approved for the treatment of rheumatoid arthritis. Remicade is currently being researched for potential usefulness in treating a range of other immune mediated inflammatory diseases, such as spondyloarthropathies, psoriasis, and ulcerative colitis. As with Xolair, Remicade has the potential to highly impact Medicare spending because of its usefulness in treating a high prevalence condition. In fact, Remicade is already among the top 10 drugs in terms of Part B spending. Arthritis and related conditions have the highest prevalence of any disease in the United States, affecting nearly 57 percent of all Americans over 70.

Antegren (generic name = natalizumab) Antegren is a third illustration of a monoclonal antibody that has important implications for multiple disease markets. Antegren is currently undergoing clinical trials by Élan and Biogen for the treatment of Crohn's disease and multiple sclerosis. Antegren is a humanized monoclonal antibody, administered by intravenous infusion, which reduces the formation of new brain lesions associated with multiple sclerosis. It has also shown promising results in inducing remission in patients with Crohn's disease.

Endnotes:

¹ United States General Accounting Office. GAO-01-1118 Medicare Drug Payments. September 21, 2001.

² MedPAC analysis lays out problems with AWP-based payments for drugs. Washington Health Beat. March 2003.

³ NDAs are used for drugs, while PLAs are used for new biologicals.

⁴ Heidelberg Innovation. Biotech: Blockbuster Medicine or Bubble Economy?
<http://www.heidelberg.de/Technologiapark/archiv/DKFZPresentationHI011205.pdf>

⁵ Backgrounder: How New Drugs Move through the Development and Approval Process. Tufts Center for the Study of Drug Development.

<http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=4>

⁶ Biotechnology Pipeline Monitor – Searching for the next blockbuster. SG Cowen Securities Corporation. Schmidt, E. et al.

⁷ Demand for biologicals expected to soar in U.S. Pharmacoconomics and Outcomes News. January 15, 2003.

⁸ We were also told about innovations in the area of anticoagulants. An example is Angiomax, recently approved for use as an injectable drug (along with aspirin) for patients with unstable angina undergoing coronary angioplasty. Similar new products are under development not for coronary disease, but also for patients with deep vein thrombosis or those undergoing joint replacement surgery. To date, however, these therapies will be used in either inpatient or ambulatory surgery center settings and will not be reimbursable under Medicare Part B.

⁹ <http://money.cnn.com/services/tickerheadlines/prn/nym100.PO.02102003084625.14455.h>

¹⁰ National Health and Nutrition Examination Survey, National Center for Health Statistics. Available online at <http://pbl.cc.gatech.edu/mindy/764>

¹¹ <http://money.cnn.com/services/tickerheadlines/prn/nym100.PO.02102003084625.14455.h>

¹² CDC. Surveillance for Asthma – United States, 1980-1999. *MMWR*; March 29, 2002/51(SS01); 1-13. <http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5101a1.htm>

¹³ PRNewswire. Facts About Centocor's Remicade (infliximab).
www.biospace.com/news_story.cfm?StoryID=8054115&full=1

Appendix: Database Sources

1. CenterWatch Directory of Clinical Trials. Winter 2001. Boston, MA.
2. Medcohealth. *Drug Trend Report*. September 2002; vol 4(1).
3. MedAd News: Future Blockbusters.
http://www.pharmalive.com/medad_month/graphic/1017.asp
4. Pharmaceutical Researchers and Manufacturers of America. 2002 Survey: New Medicines in Development, Biotechnology.
<http://www.phrma.org/newmedicines/surveys.cfm?newmedsindex=52&first=biotech>
5. Pharmaceutical Researchers and Manufacturers of America. 2003 Survey: New Medicines in Development for Cancer. Available online:
<http://www.phrma.org/newmedicines/surveys.cfm?newmedsindex=13&first=cancer>
6. Pharmaceutical Researchers and Manufacturers of America. 2003 Survey: New Medicines in Development for Heart Disease and Stroke. Available online:
<http://www.phrma.org/newmedicines/surveys.cfm?newmedsindex=57>
7. Pharmaceutical Researchers and Manufacturers of America. 2003 Survey: New Medicines in Development for Older Americans. Available online:
<http://www.phrma.org/newmedicines/surveys.cfm?newmedsindex=40&first=olderamericans>
8. The Pink Sheet. December 30, 2002; Volume 64(052), page 16
9. *Oncology R & D: Exploiting New Molecular Targets Is Challenge for 2003*. The Pink Sheet: Prescription Pharmaceuticals and Biotechnology. 30 December 2002.
10. <http://www.biospace.com/ccis/>
11. <http://www.centerwatch.com/patient/cwpipeline>
12. <http://www.phrma.org/newmedicines>
13. <http://www.pdr.net>

NOTE: In addition to these searches, we initially searched individual newsletter articles from The Pink Sheet, Centerwatch and Scrips as well as the tables of contents for relevant Wall Street analyst reports. We found substantial overlap between developmental drugs and biologicals uncovered through this process and those pulled from the existing free summary reports listed above. Also, websites listed as the last four entries were used primarily to confirm or revise developmental phase for product identified. From these sources, we learned about the recent status of drugs listed as developmental in documents published over the last two years.