



Amgen  
1300 I Street, NW; Suite 470E  
Washington, DC 20005  
202 354.6100  
Fax 202.289 7448  
Email [dbeier@amgen.com](mailto:dbeier@amgen.com)  
[www.amgen.com](http://www.amgen.com)

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[Docket No. 2004S-0233]  
Department of Health and Human Services  
Solicitation of Comments on Stimulating Innovation in Medical Technologies  
Federal Register, May 24, 2004

Division of Dockets Management  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852.

Department of Health and Human Services:

The topic of innovation is an important one to the Department of Health and Human Services for many reasons. The Department plays a central role in maintaining an appropriate environment to foster biotechnology innovation. The Department funds and leads major biomedical research efforts (especially at NIH), approves the marketing of products (FDA), delivers health care (Public Health Service), sets coverage and payment policy for Medicare and Medicaid which private insurers follow (CMS) for a substantial percentage of all therapies, and promotes the use of new medical therapies, diagnostics and infrastructure, both directly and indirectly through the FDA, CDC and AHQR, and through multiple entities with respect to electronic medical records.

The topic of innovation is vitally important to Amgen as well. Amgen's mission is to serve patients by discovering, developing and delivering innovative human therapeutics. For the past quarter century, Amgen has pioneered the development of novel medicines based on advances in recombinant DNA and molecular biology. In the 1980s, the company discovered two of the first biologically derived human therapeutics, EPOGEN<sup>®</sup> (Epoetin alfa) and NEUPOGEN<sup>®</sup> (Filgrastim), and they became the biotechnology industry's first blockbusters. Today, Amgen is the world's largest biotechnology company, producing six major therapeutic products. These also include Enbrel<sup>®</sup> (etanercept), one of the first monoclonal antibody products, indicated to treat serious autoimmune disorders such as rheumatoid arthritis and psoriasis, and Sensipar<sup>®</sup> (cinacalcet HCl), a small-molecule therapeutic indicated for the treatment of secondary hyperparathyroidism. Each year, Amgen invests approximately 20 percent of its sales back into R&D (a total of nearly \$1.7 billion in 2003) in an effort to discover and develop new breakthrough medicines for serious illnesses including cancer, osteoporosis and metabolic diseases. Amgen has built its success on values that include a dedication to science and ethics and a spirit of teamwork and collaboration. With these values as guiding principles, the company is committed to continuing to lead biotechnological innovation in the future. In line with that commitment, Amgen is pleased to have this opportunity to provide comments to HHS on how its agencies can work together effectively to continue to stimulate innovation. We

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welcome the commitment of Secretary Thompson and the leaders of HHS to view its role in innovation in a holistic fashion.

The Federal government plays vital roles in health care innovation as creator of knowledge, standard setter, payer and promoter of both technology and public health. HHS has several very important initiatives underway to support continued innovation that Amgen recognizes, such as the NIH Road Map, the Vision for the Future of Genomics Research, and the FDA Critical Path Initiative. However, it is important to keep in mind that government's roles and policies do not exclusively influence the pace, direction and magnitude of innovation in health care. The private sector and academia play vital roles as well. The academic community provides well-trained graduates for the private sector and government, Research and Development (R&D) facilities, and technology transfer roles, among other functions. How, at what level, and in what magnitude the university community commits itself to innovation in health care and responds to market and government incentives is important to securing a robust innovation agenda. Equally importantly, the private sector must organize itself effectively and apply appropriate ethical standards before it will be possible to secure optimal levels of innovation. For the US to sustain its leadership in biotechnology innovation in an increasingly competitive global marketplace, the inter-relationships and factors supporting innovation must be re-evaluated, and strengthened considerably.

For the US to maintain competitiveness in the global economy, innovation is a critical factor. In fact, the Council on Competitiveness suggests that innovation must become a national strategic priority to ensure the nation's economic strength and security. The challenges to creating a competitive innovation agenda are beyond the scope of the questions posed by HHS, but important nonetheless. Many of these issues will be addressed in the pending study on innovation by the Council on Competitiveness (to be issued December 15th, 2004).

### ***There Are Several Factors HHS Must Consider to Maintain US Leadership in Biotechnology Innovation***

The national capacity or potential for innovation is impacted by several factors, foremost of which are investment, policy choices, scientific knowledge and technological progress. Public policies related to education, training, research and development, fiscal and monetary policy, intellectual property, taxation, and market access influence our ability to generate innovation and respond to the demand for innovation. As HHS comprises several agencies critical to impelling ongoing innovation in the US, its investment decisions and policy choices will have a profound and sustained impact. A strong and fertile US innovation infrastructure requires investments and policy choices that must be sustained over decades, and thus HHS must recognize that its policy choices made today will substantially impact the future of healthcare innovation in the US for decades to come. In biotechnology, the US regulatory environment is overseen largely by the FDA in drug development and CMS in coverage and reimbursement. These agencies have influence over the time to approval of products and their diffusion, which affects the cost of innovation and the incidence and breadth of innovation. R&D investments flow to countries seen as the most fertile locations for innovation, and any uncertainty or over-regulation in these critical areas will divert investment from the US.

Biotechnology research is a global endeavor, yet nearly 75% of all biotechnology therapy patents have originated in the US. This is a reflection of the strong innovative capacity in the US, and a favorable public and private environment that must be maintained by thoughtful decisions and policy choices on the part of HHS. Biotechnology innovation is supported by the national innovative capacity, which relies in large part on access to capital markets and is driven by the potential for significant financial reward. R&D is fueled by government and private investment, broad coverage and reimbursement policies that support technology diffusion, and

strong intellectual property policies that assures that innovators may participate in the financial reward. Conversely, stimulus for investment in R&D is undermined by policies that threaten the availability of these returns, and policies that result in confusion or uncertainty regarding the probability of achieving such returns.

### ***Successful Biotechnology Innovation Requires Substantial Investment and Risk to Produce Products that Transform Patients' Lives***

New medicinal products, research techniques, medical procedures, screening tools, and prevention strategies have substantially improved the identification and treatment of human disease. During the 20th century, the United States population experienced a dramatic 29-year increase in life expectancy, attributable in part to major advances in biotechnology. These advances have resulted in substantial benefits to society, including reductions in hospital and nursing home stays; increases in social and workforce productivity among those with chronic disease; improvements in well-being and mobility in the elderly; and improvements in overall quality of life in the general population. Disability rates in people over 65 declined 25% in the last 20 years, thanks in part to medical innovations. As the Baby Boom generation reaches their senior years, they may look forward to those years being longer, healthier and more productive.

The biotechnology industry has brought life changing treatments to patients with cancer, end-stage renal disease, autoimmune disease (multiple sclerosis), and chronic inflammatory conditions (rheumatoid arthritis and psoriasis), as well as a host of other debilitating conditions. These treatments prolong life, reduce morbidity, improve quality of life, and increase social and workforce productivity. Clearly, biotechnology innovation is different from innovation in other industries in the nature and magnitude of its benefits. However, it also has a longer timetable and greater risks. According to the Biotechnology Industry Organization, it can take up to 15 years to discover and develop a new biologic intervention. Biotechnology therapy research is also an endeavor with high levels of risk. The industry estimates that for every 5,000 medicines created, only five ever progress to human clinical trials, and of those, only one will ever reach market. The industry's products are highly regulated during both development and marketing. Substantial financial investments are required to bring new products to market and support their diffusion into the market. As a result of the large investments required, the long time horizon and the inherent risk, biotechnology R&D investment – and the resulting innovation – is extremely sensitive to changes in the public policy environment.

### ***To Foster Innovation, HHS Should Focus on Streamlining the Drug Development Process and Creating Transparent and Predictable Coverage and Reimbursement Policy***

Investment in biotechnology innovation is affected by the time required to bring a product to market and the coverage and reimbursement environment the product will face when it reaches market. The presence of uncertainty in the drug development process or in the coverage and reimbursement policy environment will have a significant impact on investment in R&D. During the 1994 healthcare reform debate, the mere threat of price controls resulted in 13 of 16 startup biotechnology companies withdrawing their public offerings, and a dramatic reduction in R&D investment.

### ***Summary of Amgen Recommendations***

HHS plays a central role in developing and maintaining the national capacity for biotechnology innovation. Investment decisions and biotechnology development decisions are intrinsically linked with the degree of certainty and predictability in the regulatory development process for R&D as well as coverage and reimbursement policy. With that in mind, Amgen recommends

that HHS carefully consider the impact of agency policies on the factors that support innovation. Specifically, in the comments that follow, we will recommend that HHS:

1. Carefully consider, prior to implementation, the effect of its policies on investment in R&D spending, broad coverage and reimbursement, and intellectual property protection.
2. Continue and supplement efforts to encourage technology advancements (NIH Roadmap) and streamline the drug development process (FDA Critical Path).
3. Develop coverage and reimbursement policies in a transparent, consistent and predictable manner with the goal of an appropriate system of rewards, and the ability to focus innovation in the areas of the greatest unmet medical need.
4. Consider the patient perspective and societal values when developing policies that may affect resource allocation and avoid the untoward consequences of arbitrary government price controls that would stifle innovation.
5. Develop policies that facilitate the recognition of the value of biotechnology.
6. Develop policies that facilitate the rapid diffusion of effective innovative technology.
7. Develop a healthcare IT infrastructure to enable more effective technology assessment and flow of evidence-based information to optimize quality of care.
8. Support policies that strengthen intellectual property rights

***HHS Must Continue and Supplement Efforts to Encourage Technology Advancements and Streamline the Drug Development Process***

Amgen welcomes the NIH and FDA initiatives that will advance technology and facilitate improved development timelines.

**NIH Roadmap**

We are hopeful that the NIH Roadmap objectives of accelerating fundamental basic science discovery and translating that knowledge into effective prevention and treatment strategies will be achieved. Building the research teams of the future – teams that will include interdisciplinary research, high-risk research, and public-private partnerships – will elevate healthcare innovation to new levels.

**National Human Genome Research Institute (NHGRI)**

The NHGRI Vision for the Future of Genomics Research Long Range Plan is a bold plan to provide access and translation of the Human Genome map to the broad scientific community to improve biological science, health care and society as a whole. Public-private partnerships have been valuable in mapping the Human Genome; their continuation would benefit patients by facilitating and accelerating innovative diagnostic and therapeutic advances (the potential is enormous, as only 1% of the genes have so far been investigated for possible use).

**FDA Critical Path**

The FDA Critical Path initiative is a well-conceived plan to streamline the drug development regulatory process: a critical way to reduce the timeline for drug development and a sure stimulus to R&D investment and innovation. One of the major hurdles for this initiative will be funding it at an appropriate level to achieve success.

In response to the FDA request for written comments on the Critical Path initiative, Amgen outlined six priority areas to address drug development hurdles (Critical Path Initiative [Docket

No. 2004-N-0181]; submission number EMC 5). These potential Critical Path opportunities are listed in rank order as follows:

1. The validation and use of new technology as endpoints in clinical research studies would align the FDA with the clinical medical community. PET Scans and protein markers are two examples where the ability to track tumor progression is more sensitive than crude measurements such as overall survival.
2. More frequent and more effective use of pharmacokinetic/dynamic bio-mathematical models is beneficial in predicting the early success of a product. Opportunities exist with these models for the FDA to change the regulatory environment around early product feasibility by participating in the development of methods, and supplying data to assist in the formation of PK/PD models. The FDA should work with industry and academia to develop improved methods and a library of case studies.
3. Pharmacodynamic and pharmacokinetic assays are rarely used in combination in early clinical research to assess the potential therapeutic benefit and adverse events. The regulatory environment must change to meet the scientific challenge of developing sensitive, specific PD assays relevant to a particular molecular target and/or pathway in human disease.
4. Models to predict toxicity that correlate chemical structure with potential adverse events and clinical outcomes are becoming more widely available and used. The development of these models would benefit both pre- and post-marketing evaluations of adverse event profiles; the FDA should be involved with developing these models.
5. FDA needs to determine how new genomic technology will be incorporated into both drug development and post marketing surveillance. The advance in genetics has created and will continue to create new ways to identify patients with rare diseases or who could be susceptible to rare side effects. A new discipline, toxicogenetics, is quickly being incorporated into clinical practice and provides promise for the drug development process.
6. Clinical trial execution needs to be streamlined in four areas, listed by priority: 1) Serious Adverse Event (SAE) reporting; 2) clinical trial investigator and patient recruiting; 3) Updating regulations; and 4) Recording and storing medical records electronically. The FDA needs to take an active approach to ensuring more efficient development of new drugs.

(As these areas were detailed in our earlier comments to HHS in our critical path submission, we refer you to that document for a more detailed discussion.)

***HHS Must Implement Transparent and Predictable Coverage and Reimbursement Policy and Avoid the Untoward Consequences of Government Price Controls***

It is well accepted that streamlining the drug development process is critical to facilitating and fostering innovation. However, the impact of coverage and reimbursement policy on biotechnology innovation is less well understood. Coverage delays, price controls, and restrictive reimbursement policies have become commonplace in Western and Central European and Asian countries, where free-market principles are not upheld. This has had a chilling effect on both technology diffusion and innovation. HHS has acknowledged that restrictive regulatory policies in the US would have a similar impact: "If applied broadly in the United States, government-controlled restrictions on the coverage of new drugs could put the future of medical innovation at risk and may retard advances in treatment and in the development and introduction of new products. Moreover, government controls may reduce or delay access to specific drugs for seniors." Likewise, price controls have been shown to stifle innovation and result in increased drug prices.

Medicare coverage and reimbursement policies for most biotechnology products are frequently subjected to processes and cost containment tools that are neither consistently applied nor sufficiently transparent. This creates significant marketplace uncertainty and impedes the ability to forecast future revenues, all of which impact the ability to attract investment from the capital markets. Moreover, uncertainty and inconsistency in reimbursement policy can affect provider willingness to utilize injectable products, which impacts patient access. This uncertainty not only affects existing products, but also impairs the ability to make effective decisions in early drug development and to forecast the long-term financial potential of mid- to late-stage development projects. Transparent, consistent and predictable coverage and reimbursement policy will facilitate drug development and investment decision-making, which should result in a more productive biotechnology enterprise.

The development of new biotechnology products is a high-risk, hugely expensive undertaking. HHS should develop coverage and reimbursement policies that explicitly recognize this fundamental reality in two ways.

1. it is necessary to offer coverage, reimbursement and payment policies that offer sufficient financial returns to justify continuing research efforts.
2. While there are some important new products that constitute paradigm-shifting improvements in patient care and they deserve robust reimbursement, it is inappropriate to offer full reimbursement only to such products. There are other substantial improvements that flow from incremental developments that, in their cumulative effect, offer real and important advances in patient care. Increasingly, in an era of accelerating personalization of care, it is important to recognize the benefits of such advances to individual patients and their caregivers.

As US coverage and reimbursement policy evolves, the population ages, and pressure increases to control expenditures, HHS should abide by several principles to assure that policies do not retard investment in biotechnology R&D, thereby stifling innovation. Specifically:

- HHS should encourage a coverage and reimbursement system that avoids the arbitrary price-setting and coverage delay processes employed in other countries.
- HHS should develop a system of appropriate rewards that recognizes products that address previously unmet medical needs and improve quality of care.
- Innovative products should be accessible to the broadest population of patients with a particular condition.
- HHS should insist that CMS employ only authorized policies, and utilizes transparent and consistent coverage and reimbursement decision-making using established methods and standards.
- Changes to coverage and reimbursement policy should follow an appropriate period of public comment and open dialog.
- Standards for evidence need clear definition and should not be based solely on clinical trials or on narrowly constructed formulaic methods that are easily misinterpreted and misused, or that could limit the appropriate diffusion of the innovation.
- Attempts by HHS to develop innovation criteria, necessary and reasonable criteria, or “substantial improvement” definitions should incorporate a broad array of clinical and patient-centered outcomes, and should be defined in disease-specific categories utilizing independent, unbiased panels of experts who understand the significance of the innovation.
- When important innovation is present, CMS should participate in establishing such products as the standard of care through guidelines, pay-for-performance rewards for high quality care, and reduced barriers to patient access.

- CMS should take a broad perspective in coverage and reimbursement decision-making, considering the ways in which utilizing technology earlier in the course of disease may reduce the overall burden of cost to Medicare.

As coverage and reimbursement policies are developed within HHS, careful attention should be paid to the aforementioned principles to assure that open, transparent, consistent and predictable decision-making processes are in place to facilitate effective drug development research decisions and stimulate investment in R&D.

### ***HHS Should Develop Policies That Define the Value of Treatment from the Patient Perspective***

The true value of healthcare interventions is not well understood by payer communities, providers or patients. In part, this is due to the fragmentation of the health care delivery system, in which financial silos exist such that a holistic view of the economic impact of interventions is not recognized. For example, a payer with a pharmacy budget who is reimbursing the cost of a specific medication cannot account adequately for the cost savings gained by avoiding or reducing time in hospital due to the use of that medication. Traditionally, payers or insurers have focused on cost-minimizing, rather than viewing biotechnology therapy as an investment in health, because they have not been able to account for or directly realize such an investment in terms of social and work-related productivity, patient quality of life, or economic benefits found elsewhere in the delivery system. The current approach has promoted a competitive environment that has become a zero-sum game: saving costs in one part of the health care system by shifting costs to other parts. But this game is in fact not a “zero-sum” proposition: It actually increases overall costs to the health care system.

The primary beneficiary of healthcare interventions, the patient, has not traditionally been involved in assessing the value of healthcare interventions. The complex interactions of medical providers, insurance companies and employers within the medical system ultimately force the value assessment to occur at the insurer-provider level. Going forward, payers should consider how patients value healthcare interventions as they make resource allocation decisions and trade-offs. Priorities and values elicited from patients should inform resource allocation decisions made by government payers, particularly CMS. This elicitation of values should be done using scientifically accepted methods, and performed in an open and transparent fashion. Until the patient is more completely involved in the process of assessing the value of healthcare interventions, the “value” of new innovation will continue to be narrowly defined in terms of immediate cost, rather than overall investment, which could negatively impact coverage decisions and future investments in innovation.

HHS must consider a broad and patient-centered method for assessing the value of innovation, so that coverage and reimbursement decisions may be made with this in mind. HHS should also carefully consider such issues as the Part D drug benefit is implemented, and the value of therapies will impact formulary choices.

### ***HHS Should Facilitate the Rapid Diffusion of Effective Medical Technology Through Appropriate Policy and the Deployment of an IT Infrastructure***

An additional barrier to the facilitation of innovation is the rate of technology diffusion. Technology diffusion is a result of multiple factors, including discovering ways to apply new science, disseminating new knowledge and applied technology to workers and institutions, time and costs of development and approval, ability to gain coverage and reimbursement, and uptake by insurers and providers based on the perceived value of a new intervention. Without rapid technology diffusion, the financial risk of investment may outweigh the benefit, which

would dramatically slow the pace of innovation. Evidence of this effect is seen in Western and Eastern European countries, which employ significant coverage delays of new products as a cost-containment tool.

Adequate technology diffusion can affect future investment in biotechnology; thus the pace of innovation is greatly influenced by the policies of the various HHS agencies. The speed of innovation diffusion is intrinsically related to coverage and reimbursement decision-making and to assessing the value of healthcare interventions. When value is properly evaluated, more informed coverage decisions are possible. HHS agencies should avoid the restrictive price controls and coverage delays employed by other countries. This will ensure rapid diffusion of effective technology to promote patient care and public health and maintain an appropriate incentive for investment in innovation. HHS agencies can and should assist one another, the healthcare providers, and the public in understanding the value of innovation by educating the public about new medical science, promoting public health, determining effective methods to measure diseases and informing the public about the quality and effectiveness of new interventions.

To accomplish this, the health care system in the United States requires a well-designed and integrated IT infrastructure that will permit payers, providers and patients to make informed decisions. Knowledge about new and existing diseases and treatments should be shared universally. An IT infrastructure including a database of electronic medical records will enable measurement and reporting of the quality of care, and the ability (through innovation such as computerized physician order entry) to provide real-time clinical information and evidence at the "point of care", where it is needed to inform decision making. Such an integrated information infrastructure will enable to HHS to better evaluate the effectiveness and safety of products, and to traverse the many silos in the system to measure and appreciate the true value of interventions in the healthcare system.

Without access to an integrated electronic medical record-based dataset, only parts of the patient population can be evaluated for research questions, and the population of patients who could benefit most from the use of a new product cannot be easily identified and assessed. Early knowledge of the successes or failures of a new product could affect its continued diffusion and help identify early issues in compliance or safety. Since there are significant gaps in the quality of care, many of which are due to underutilization of technology, an IT infrastructure is critically important to quality improvement efforts at the national level. An IT infrastructure would facilitate the more rapid identification of quality gaps and provide more focused investments in innovation to fill those gaps. An appropriate system of rewards, as discussed previously, could help HHS direct investment toward innovation.

For these reasons, Amgen supports the creation of the proposed National Medical Information Technology Infrastructure, and believes it will be critical for identifying value in medical care. The innovation process will be stimulated through improved scientific exchange, better disease level information, and an improved national dataset on clinical disease. All of these will help identify the unmet medical needs of the patient for which innovation will continue to be targeted.

### ***HHS Should Support Policies That Strengthen Intellectual Property Rights***

Amgen would also like to see the HHS support a strong intellectual property system. Recently, both the Federal Trade Commission and the National Academy of Sciences have issued reports on the American intellectual property system. While we do not agree with all of the recommendations in these reports, we recognize that improvements are necessary to improve the quality of issued patents, and to enhance the processes for adjudicating key intellectual property rights. We want to work with HHS and others to make sure that the vital role of

intellectual property to our industry is fully understood and reflected in HHS policy. Intellectual property protection is, according to respected academic experts, demonstrably more important to biotechnology therapies and our efforts at innovation than to any other industrial sector.

**Summary of Amgen Recommendations**

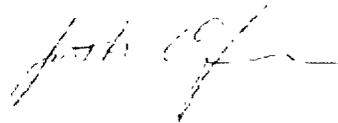
Amgen appreciates the opportunity to provide comments on the Innovation Solicitation. We look forward to engaging with HHS and other stakeholders in a meaningful partnership to continue to lead the global marketplace in innovation, and to develop new medical breakthroughs that will transform patients' lives. To achieve the HHS objectives of having agencies work together to stimulate medical technology innovation, Amgen recommends that HHS:

- ◆ Carefully consider, prior to implementation, the effect of its policies on investment in R&D spending, broad coverage and reimbursement, and intellectual property protection.
- ◆ Continue and supplement efforts to encourage technology advancements (NIH Roadmap) and streamline the drug development process (FDA Critical Path).
- ◆ Develop coverage and reimbursement policies in a transparent, consistent and predictable manner with the goal of an appropriate system of rewards, and the ability to focus innovation in the areas of the greatest unmet medical need.
- ◆ Consider the patient perspective and societal values when developing policies that may affect resource allocation and avoid the untoward consequences of arbitrary government price controls that would stifle innovation.
- ◆ Develop policies that facilitate the recognition of the value of biotechnology.
- ◆ Develop policies that facilitate the rapid diffusion of effective innovative technology.
- ◆ Develop a healthcare IT infrastructure to enable more effective technology assessment and flow of evidence-based information to optimize quality of care.
- ◆ Support policies that strengthen intellectual property rights

Sincerely,



David Beier  
Senior Vice President  
Global Government Affairs



Joshua J. Ofman, M.D. M.S.H.S.  
Vice President  
Reimbursement and Payment Policy

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