Recombinant Erythropoietin: Payment Options for Medicare

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RECOMBINANT ERYTHROPOIETIN: PAYMENT OPTIONS FOR MEDICARE

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FOREWORD

Recombinant erythropoietin represents a therapeutic breakthrough in the treatment of anemia. Using biotechnology, researchers have developed a recombinant form of the hormone erythropoietin, which stimulates the production of red blood cells. The biologic corrects anemia associated with chronic renal failure and is being studied for its possible use in other medical conditions. Recombinant erythropoietin not only reduces patients' need for blood transfusions but also alleviates symptoms of anemia and improves the quality of their lives.

Policy interest in Medicare's payment policies regarding recombinant erythropoietin has arisen chiefly because of the biologic's expense. Through the End Stage Renal Disease program, Medicare covers the biologic for more than **90** percent of the country's approximately 100,000 patients who require dialysis. At Medicare's current payment rate, an annual supply of the product may cost $5,000 to $6,000 per treated patient.

Because of concern about the implications of recombinant erythropoietin use for Medicare expenditures, the House Ways and Means Committee, Subcommittee on Health, requested OTA to examine alternative payment policies that Medicare might adopt to pay for the biologic. In responding to that request, this Special Report reviews clinical and economic issues regarding the use of recombinant erythropoietin and develops a series of options for Congressional consideration.

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INTRODUCTION

The Food and Drug Administration's (FDA) approval of the biologic[1] recombinant erythropoietin in June 1989 made available an important therapeutic advance for treating anemia associated with chronic renal failure.[2] By increasing the body's production of red blood cells, recombinant erythropoietin may correct anemia and reduce the need for blood transfusions, the most frequently used treatment for this condition.

Although recombinant erythropoietin has engendered excitement in the clinical community, it has also produced concern among policymakers because of its expense and the financial implications for the Medicare program. An annual supply of the product may cost approximately $5,000-$6,000 per treated patient. Because Medicare covers medical services for the elderly and disabled and for about 100,000 dialysis patients (156), it is by far the predominant payer for recombinant erythropoietin in the United States.[3]

Reflecting concern about increased Medicare expenditures, the House Committee on Ways and Means, Subcommittee on Health, requested the Office of Technology Assessment (OTA) to evaluate alternative payment policies for Medicare that might control expenditures related to recombinant erythropoietin without sacrificing the quality of care for beneficiaries.[4] This Special Report responds to that request.

This chapter first summarizes background material regarding recombinant erythropoietin and then identifies and analyzes options for Medicare payment of the biologic. Chapter 2 analyzes the clinical literature on its efficacy and safety; chapter 3 describes the economics of the recombinant erythropoietin marketplace; and chapter 4 reviews Medicare's current payment policies for services provided to patients with end-stage renal disease,[5] for other pharmaceuticals, and for recombinant erythropoietin administered in different health care facilities. The appendixes contain supporting material: appendix A describes the method used to conduct the study; appendixes B and C acknowledge the valuable assistance of workshop

1 FDA defines a biologic as any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of disease or injuries to humans (21 CFR 600.3h).

2 Chronic renal failure is a degenerative condition that progresses from a predialysis phase, during which the kidneys still maintain some of their function, to a later phase, when a continuous course of dialysis or kidney transplantation is needed to maintain life. Anemia is characterized by a significant decrease in red blood cell mass and a decrease in the oxygen-carrying capacity of the bleed (23). Anemia is a common complication of chronic renal failure and, in patients with that condition, is caused primarily by an insufficient production of the hormone erythropoietin.

3 In February 1990, Medicare contractors processed claims for recombinant erythropoietin therapy from dialysis facilities for about 31,000 patients. These claims totaled $16.9 million, of which Medicare's share was 80 percent or $13.5 million (47).

4 This study was originally requested as part of a broader OTA project to evaluate alternative payment policies that Medicare could adopt for the outpatient prescription drug benefit added by the Medicare Catastrophic Coverage Act of 1988 (Public Law 100-360). After that benefit was repealed, OTA's Congressional Technology Assessment Board rescinded its approval of the broader study.

5 End-stage renal disease refers to permanent, chronic kidney disease requiring continuous dialysis or a kidney transplant to maintain life.

participants and other individuals; appendix D defines technical terms in a glossary; and appendix E describes the method that the Office of the Inspector General used to estimate the costs related to recombinant erythropoietin of Amgen Inc., currently the only manufacturer that FDA has approved to market the biologic.

SUMMARY

Clinical Significance of Recombinant erythropoietin

FDA evaluation of the safety and efficacy of recombinant erythropoietin was based on data from clinical trials conducted in the United States in anemic chronic renal failure patients. For predialysis and dialysis patients, efficacy data indicate that the biologic increases hematocrit levels and reduces blood transfusions in most patients. The rate of increase in hematocrit and the time required to increase it depend on the dose. The product appears to be efficacious by both the intravenous and subcutaneous routes of administration. The optimal level of initial and maintenance doses, however, still require investigation.

The quality of life of dialysis patients has been impaired because of a number of factors, including the symptoms of anemia (59). Studies assessing the effect of recombinant erythropoietin on the quality of life of chronic renal failure patients suggest that recombinant erythropoietin improves the well-being and ability to function of dialysis and predialysis patients. Future studies should determine long-term changes in the quality of life in elderly dialysis patients, the group projected to have the fastest rate of growth in the dialysis population in the near future, and the ability of dialysis patients to return to work. In addition, the relationship between the use of recombinant erythropoietin and the delayed need for dialysis in the predialysis population should be studied further.

Recombinant erythropoietin appears to be relatively safe. Hypertension is the most frequently occurring adverse reaction (160). Although seizures have been reported, they seem to occur at about the same rate in untreated patients. Information is not available, however, on whether the incidence of any adverse reaction is statistically different compared with untreated patients. Many of the side effects attributable to recombinant erythropoietin therapy, such as hypertension, may be the result of the natural progression of chronic renal failure.

The occurrence of hypertension in treated patients is a particularly important side effect, since the majority of chronic renal failure patients already have high blood pressure (38). The incidence of seizures, although not significantly different from untreated patients, appears to occur most frequently during the early stages of therapy as the hematocrit is increasing (160). Iron deficiency occurs because iron is necessary for erythropoiesis, the process of red blood cell formation (23).

Studies are underway to evaluate the use of recombinant erythropoietin for other anemias, including anemia associated with human immunodeficiency virus (HIV), rheumatoid arthritis, and cancer. The efficacy of recombinant erythropoietin in increasing the donation of autologous blood prior to elective surgery is also under investigation.

The Structure of the Recombinant erythropoietin Marketplace

Scientists have long recognized the medical importance of erythropoietin in regulating red blood cell production. erythropoietin was first purified from human urine in 1977; however, naturally-produced human erythropoietin was an unacceptable treatment alternative because of an inability to collect and adequately purify sufficient quantities for human administration (102).

In the mid 1980's, several biotechnology firms attempted to make erythropoietin for therapeutic use. Two of the manufacturers were Amgen Inc., of Thousand Oaks, CA and the Genetics Institute of Cambridge, MA. Amgen developed and patented genetic material that is an important component needed for the production of recombinant erythropoietin in Chinese hamster ovary (CHO) cells. Genetics Institute developed and patented a method to purify erythropoietin (6).

To market recombinant erythropoietin in the United States, each manufacturer entered into a licensing agreement with other manufacturers. Except for chronic renal failure patients on dialysis, Amgen Inc. licensed its domestic rights for recombinant erythropoietin to the Ortho Pharmaceutical Corporation of Raritan, NJ. Genetics Institute licensed its domestic rights to Chugai Pharmaceutical Company of Japan, which in turn licensed its U.S. rights to Chugai-Upjohn, Inc., of Rosemont, I1, a joint venture of the Chugai Pharmaceutical Company of Japan and the Upjohn Company of Kalamazoo, MI. Continuing disputes over patent rights between Amgen Inc. on the one hand and Genetics Institute and Chugai on the other, and over the licensing agreement between Ortho Pharmaceutical Corporation and Amgen Inc. have resulted in legal proceedings that are still unresolved. The results of these proceedings have major implications for the number of suppliers of recombinant erythropoietin that will be on the market.

The Orphan Drug Act of 1983 provides incentives for manufacturers to develop products for rare diseases, currently defined as conditions afflicting fewer than 200,000 individuals in the United States. When a sponsor files an application for FDA to approve a new product for marketing, the sponsor may also apply for FDA to designate the product an orphan. Several sponsors of the same product may receive orphan designations for the same rare condition, but FDA grants a 7-year period of market exclusivity for that condition only to the sponsor who first receives FDA approval to market the product. To date, FDA has approved only Amgen's Epoetin alfa and has granted 7-year market exclusivity only to Epoetin alfa for anemia associated with chronic renal failure.[6]

Ortho's product has orphan designation for the use of recombinant erythropoietin for anemia associated with HIV[7] and with preterm infancy (54 CFR 16295). A product may have orphan drug designation and obtain market exclusivity for multiple

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6 FDA will refer to recombinant erythropoietin in general as **Epoetin** and will add the suffix **alfa,** beta, or gamma, etc. for different recombinant erythropoietin (160). At the time of this Special Report, the United States Adopted Names Council, the organization charged by FDA with assigning names to new compounds, had assigned the name **Epoetin alfa** to **Amgen's** product and **Epoetin** beta to Chugai-Upjohn's product. FDA, however, which makes the final determination on names assigned to new products, had not assigned **Epoetin** beta to any product.

7 **Ortho** submitted a Product Licensing Application **(PLA)** to the FDA in February 1989 for this indication (l).

orphan conditions. Thus, if approved by FDA, Ortho's product could receive 7-years of market exclusivity for recombinant erythropoietin for these two conditions.

In addition, Ortho's and Chugai's products have each received orphan designation for anemia associated with ESRD. Structurally different products may receive 7 years of market exclusivity for the same orphan condition. If FDA finds either product structurally different from Amgen's, that company's product could theoretically be granted 7 years' exclusivity for anemia associated with ESRD or chronic renal failure.[8] By April 1990, FDA had not determined whether Chugai's or Ortho's product is different from Amgen's (142).

The existence of multiple patents, the licensing agreements made among the manufacturers, and the granting of exclusivity as orphan products to multiple brands of recombinant erythropoietin have the potential to increase the sources of supply of recombinant erythropoietin. Ortho's product, Eprex, and Chugai-Upjohn's product, Marogen, maybe on the market shortly, joining Amgen's product, Epogen. Although one might expect that the existence of competitors would lower the price of recombinant erythropoietin available to Medicare and its beneficiaries, lower prices have not necessarily followed the entry of additional manufacturers into the markets for other pharmaceuticals (100a).

Medicare payments currently dominate the domestic market for recombinant erythropoietin and constitute the primary source of revenue for Amgen, the sole manufacturer. The Medicare program will remain the predominant payer of recombinant erythropoietin for the near term, giving it substantial leverage in the marketplace, especially if there are multiple sources of supply.[9]

Medicare's Current Payment Policies

For covered beneficiaries, the Medicare program currently pays for recombinant erythropoietin administered to dialysis patients in dialysis facilities and to dialysis and predialysis patients in physicians' offices. Because the Social Security Act generally prohibits Medicare from covering pharmaceuticals that are self-administered, Medicare does not cover recombinant erythropoietin that patients administer to themselves. This restriction prevents Medicare from covering self-administration for patients who receive dialysis at home, who could number up to 18,000 beneficiaries (124).[10]

For recombinant erythropoietin administered in a dialysis facility, Medicare has set a rate of $40 for any dose under 10,000 units administered to increase a patient's hematocrit to a target level of 30-33

8 Amgen's original orphan product designation was for the use of recombinant erythropoietin for anemia associated with ESRD. Market exclusivity, however, was awarded to Amgen for the broader indication of chronic renal failure. Ortho and Chugai-Upjohn have tiled PLAs for chronic renal failure: it is not known whether their products will be approved for a broader indication or if the orphan drug designation will be expanded (142).

9 Since Medicare pays the medical expenses for approximately 93 percent of U.S. dialysis patients, it will continue to dominate payments for recombinant erythropoietin in this market. At present, Medicare also covers recombinant erythropoietin for elderly and disabled predialysis patients. FDA approval of the biologic for other indications under study, including anemia associated with HIV, infant prematurity, and cancer plus autologous blood donations, would add additional beneficiaries to Medicare's coverage.

10s. 2098 introduced in the Senate and H.R. 4247 introduced in the House of Representatives would extend Medicare coverage to self-administration of recombinant erythropoietin for dialysis patients.

percent, but no higher than 36 percent.[11] Medicare pays an additional *$30* for any dose over this amount needed to raise the hematocrit to the target level (154). The Health Care Financing Administration (HCFA) used an estimate of Amgen's costs along with other factors in setting the payment rate (see app. E).[12] Medicare pays for recombinant erythropoietin as a separate item in addition to the composite rate paid to dialysis facilities for a package of services and supplies that are commonly used during dialysis treatment (154). Medicare does not pay dialysis facilities separately for any additional staff time or supplies, such as needles and syringes, that are used to administer recombinant erythropoietin; Medicare considers these expenses to be covered by the composite rate.

For administration in a physician's office, Medicare pays for recombinant erythropoietin on a fee-for-service basis and sets approved charges based on customary, prevailing, and reasonable Charges.[13] Medicare makes a monthly capitated payment, which currently averages $173, to the physician supervising the patient's dialysis-related care. For recombinant erythropoietin and other pharmaceuticals, Medicare pays these physicians an additional amount only for the product and the supplies to administer it; it considers payment for staff time to administer the product to be covered by the monthly cavitation payment. If the physician administering recombinant erythropoietin is other than the patient's capitated physician, Medicare pays for the product and supplies, and that physician must obtain reimbursement for staff time from the capitated physician (155).

Available data suggest that payments to dialysis facilities have been covering their costs. According to claims for dialysis patients processed through February 1990, the dose per treatment has averaged about 2,700 units, and Medicare's approved charge has averaged about $41 per treatment (47).[14] Based on a survey of selected dialysis facilities from November 1989 through March 1990, their product cost per treatment has averaged about $28 (slightly over $10 per 1,000 units) (85). According to one facility, its costs of labor, supplies, and financing amount to about $4 per treatment (43,90).1[5] If these non-product costs are representative of dialysis facilities generally, costs per treatment

l1 For doses under 10,000 units, Medicare's actual payment to the dialysis facility is $32 per administration, since the program covers 80 percent of the approved charge for medical semices under Part B, and patients pay the remaining 20 percent as cost sharing. At this payment rate, annual per patient costs for recombinant erythropoietin could total $6,240, 80 percent of which, or $4,992, would be paid by Medicare, and 20 percent, or $1,248, would be paid by the patient or another third-party.

l2 It was anticipated that an average of 5,000 units of recombinant erythropoietin would be administered at each of the 3 weekly dialysis sessions (129). Recent data indicate that dialysis patients are averaging 2,500 to 2,900 units per administration (47,117).

13 Determination of Medicare's approved charge is made by Medicare's contractors, known as intermediaries and carriers, based on guidelines developed by HCFA. In general, carriers make payments for outpatient services, and intermediaries make payments for inpatient services. Payment for services provided in a dialysis facility, however, are made by intermediaries, and payment for dialysis-related physician services are made by carriers. HCFA regulations define the approved charge as the lowest of 1) the physician's or supplier's customary charge for that service, 2) the prevailing charge for similar services in that locality, 3) the actual charge made by the physician or the supplier, or 4) the private business charge for comparable service (35). For injectable, Medicare advises its carriers to use prices from certain compendia of information on pharmaceutical prices to set the approved charge (155).

IL Through February 1990, HCFA contractors had processed claims submitted by about 1,400 dialysis facilities for about 31,000 patients (47).

I5'l%ese additional costs are based on current estimates for one dialysis facility in Michigan. The representativeness of this cost is not known. The facility was involved, over a 2-year period, in Amgen's clinical trials for recombinant erythropoietin. Therefore, their non-product costs are based on considerable experience in administering this biologic and may also incorporate practices continued after the clinical trials ended. Their figures did not include an allowance for fixed costs associated, for example, with building and equipment.

would total close to $32, and dialysis facilities would be averaging a profit of about $9 per treatment.

These statistics require certain caveats. Because of the different mix of patients at different facilities, a dialysis facility could be only breaking even or even incurring losses, if its patients required higher doses to respond. Furthermore, the data averaged from claims do not reflect the evolving nature of patient treatment and the dynamics of the patient population. Data from clinical studies suggest that the average dose for most patients may rise over time, at least during the initial phase of therapy. During the induction phase, before the target hematocrit was reached, about 55 percent of patients responded to doses equivalent to about 3,000 units per patient, but doses over 5,000 units were needed for 80 percent to respond (55) (see ch. 2). Although clinicians appear to be initiating therapy at low doses, the amounts may rise as substantial numbers of patients fail to respond. Doses required to maintain hematocrits at the target level could be much lower, however (see ch. 2).

At any time, the treated population consists of patients at various stages of therapy. At present, when diffusion of this therapy is progressing rapidly, new entrants would be expected to comprise a greater percentage of treated patients than during the later phases of diffusion, when most patients will be on a maintenance dose. Thus, it is possible that the average dose and the profits earned from current payment levels could change considerably over time. It is also possible that dosage levels have been influenced by the incentives of current payment methods to constrain use per treatment and to treat marginally anemic patients, as described below under option 3. Clarification of these patterns must await data on more long-term experience with therapy and Medicare claims.

DIMENSIONS FOR EVALUATING PAYMENT OPTIONS

Medicare coverage of medical services is intended to give beneficiaries financial access to medical care that can maintain and improve health or slow its deterioration. Medicare coverage of recombinant erythropoietin for anemic patients with chronic renal failure has improved financial access to a therapeutic breakthrough that is becoming the standard of care for this condition. In an analysis of the implications of alternative payment options, the likely effects on the quality of beneficiaries' care and on their financial access to care command primary attention. Especially in an era of Federal budget constraints, how a payment alternative is likely to affect Medicare expenditures and overall efficiency also weighs heavily in decisionmaking.

The payment options identified in this Special Report are evaluated according to their likely effects across these and other dimensions worthy of consideration: the quality of beneficiaries' medical care; access of beneficiaries to medical care; costs to the Medicare program, beneficiaries, and society plus overall efficiency; equity for beneficiaries and providers; technological innovation; and administrative feasibility. Payment methods that are effective in achieving some of these objectives may interfere with others. Highlighting these tradeoffs is an important part of the analysis in this chapter.

Quality of Care

By affecting incentives for providers and patients to use services, Medicare payment methods for recombinant erythropoietin may affect the quality of medical care that beneficiaries receive. The quality of care has many dimensions, reflecting the diversity of acceptable outcomes for patients, the complexity of the medical care process, and the multiple dimensions of patients' health.

Underlying evaluations of the appropriateness of care for a specific condition is knowledge about the efficacy and safety of a technology, such as recombinant erythropoietin, and its relationship to other technologies. Therapeutic technologies may bring about changes in length or quality of life, with effects on functional, physical, and psychological well-being. For patients with chronic renal failure, recombinant erythropoietin has been shown to correct anemia, reduce blood transfusions and improve functioning and well-being (see ch. 2). The risk of severe adverse events, such as seizures, appears to be minimal, and common side effects, such as hypertension, can usually be controlled.

Depending on the method and level of payment, Medicare policies may encourage providers to increase or decrease their use of recombinant erythropoietin and other services, with subsequent implications for patients' health. Similarly, through effects on patients' out-of-pocket expenses and access to care, payment policies may influence beneficiaries' decisions regarding the use of services and, ultimately, the quality of care received.

Access to Care

The concept of access refers to the ease with which a beneficiary can obtain medical care. Access relates to financial and physical barriers to obtaining a particular service. By affecting beneficiaries' and providers' costs, Medicare payment may influence both aspects of access.

Medicare beneficiaries directly bear the costs of recombinant erythropoietin and most other Part B services through an annual deductible and, for expenses greater than the deductible, through payment of 20-percent of Medicare's approved charge. If a physician's charge exceeds Medicare's approved charge, the physician may also bill the beneficiary for the balance. Given that treatment with recombinant erythropoietin can result in sizable out-of-pocket expenses for beneficiaries, in the range of $1,250 per year under the current payment method for dialysis patients, these direct financial liabilities may affect access to care. Although private supplementary insurance and Medicaid cover Medicare deductibles and copayments for many beneficiaries, financial access may still pose problems for some beneficiaries.[16] Therefore, payment methods that keep Medicare expenditures for recombinant erythropoietin at reasonable levels also afford greater financial access to beneficiaries.

16 According to a 1981 survey of ESRD patients, about 80 percent of Medicare patients receiving **hemodialysis** at home, 66 percent of patients receiving **hemodialysis** from a center, and 74 percent using continuous ambulatory peritoneal dialysis and continuous cycling peritoneal dialysis (both in-center and at home) had insurance coverage supplementary to Medicare's. No information was available, however, on the portion of Medicare deductibles and copayments that were covered. (94)

Medicare's payment policies may also affect how out-of-pocket expenses are distributed across beneficiaries. Payment methods that result in copayment extremes may be more harmful to access, particularly for those without Medicaid or other supplementary coverage, than methods that keep these direct beneficiary costs to more uniform levels. For example, under fee-for-service payment for recombinant erythropoietin, patients requiring high doses could incur out-of-pocket expenses many times the more uniform out-of-pocket expenses that beneficiaries now incur under the current per-treatment payment to dialysis facilities.[17]

In addition, Medicare policy may affect beneficiaries' access through restrictions on the settings in which services are covered. For example, because Title XVIII of the Social Security Act does not cover pharmaceuticals that patients administer to themselves, Medicare does not cover self administration of recombinant erythropoietin by dialysis patients in their homes. Especially for patients who receive dialysis at home, travel to physicians' offices or dialysis facilities to obtain the biologic could prove inconvenient.

Besides more direct effects on beneficiaries, financial incentives imparted by payment methods to the providers of recombinant erythropoietin may affect access. Depending on the payment method, providers may have a financial incentive to treat low-dose, less costly patients who would benefit only marginally from this biologic or to deny appropriate treatment to high-dose, more costly patients.

Costs *and Efficiency*

Costs and efficiency refer to the use of resources that are implied by a payment option, especially when measured against alternative uses to which those resources could be put. The costs of recombinant erythropoietin are directly borne by the Medicare program and, through deductibles and copayments, by beneficiaries. Indirectly, these costs are borne by society through taxes and by beneficiaries through Medicare premiums.

The total costs of recombinant erythropoietin to the Medicare program depend on the quantity consumed, Medicare's payment rate, and resulting effects on the use and cost of related medical services. Medicare's costs represent alternative uses of public and private resources and should be balanced against the health benefits gained from the biologic. Additional dollars spent on recombinant erythropoietin may be taken from other worthy areas, both public and private, to which society's limited resources may be allocated. Therefore, payment methods should encourage an allocation of resources between recombinant erythropoietin and other areas that is socially desirable.

Payment methods should also encourage distributors and providers to set prices that reflect the least-cost method of producing or providing a product and do not include a higher profit than is necessary to compensate for these activities. Higher prices

17 According to claims from dialysis facilities processed during November and December 1989, the dose per treatment with recombinant erythropoietin ranged from fewer than 1,500 units to over 10,000 units (47). If providers charged $10 for each 1,000 units, charges for the product alone would total $100 per treatment for patients receiving 10,000 units per treatment. Based on the 20-percent coinsurance for Medicare, annual out-of-pocket expenses for patients without supplementary insurance coverage could reach more than $3,000.

imply fewer health benefits from any Medicare dollar allocated to recombinant erythropoietin. By the same token, prices that are too low may discourage socially desirable investments and, depending on their pricing strategies, may induce distributors and providers to shift costs to other payers.

Historically, health insurance coverage and methods of payment have insulated providers and beneficiaries from the financial implications of their decisions to buy and use medical technologies. The literature clearly shows that use and total expenditures have been higher the lower beneficiary out-of-pocket expense when medical services are rendered (144). One would expect that the use of recombinant erythropoietin, like other expensive therapies, would be greater with Medicare coverage. Physicians would be more likely to prescribe and patients to use the biologic the lower patient cost-sharing.

Equity

Equity relates to who pays and who benefits from Medicare's policies. In public finance generally, equity is served by treating similarly people in similar circumstances and by treating differently people in different circumstances.

For recombinant erythropoietin, the issue is to what extent beneficiaries' out-of-pocket expenses should vary with their use of the biologic. For example, dialysis patients who require little or no recombinant erythropoietin may look unfavorably on a payment method that significantly increases their out-of-pocket expenses. Beneficiaries may feel that their direct payments for recombinant erythropoietin should be commensurate with their use. Historically, out-of-pocket expenses, whether for private insurance or for Medicare coverage, have varied with the use of services.

For providers of recombinant erythropoietin, equity is served if payments reflect any differences in their costs that are associated with operating in different markets. For example, some providers in small and geographically remote markets may incur higher unit costs for recombinant erythropoietin because of smaller purchases and costlier transportation expenses. Other providers of recombinant erythropoietin may serve patients who, on average, require larger doses of recombinant erythropoietin. Such market-related costs, if not incorporated into Medicare's payment rates, could adversely affect providers' finances and, in turn, beneficiaries' access to care. In addition to possible effects on beneficiaries, Government agencies have an obligation to treat providers, distributors, and manufacturers fairly, especially when the Government commands a predominant role in the market, as it does with recombinant erythropoietin.

Technological Change

Through its influence on the market, Medicare payment policies can shape the direction and extent of innovation in medical technologies. How Medicare and others pay for the services associated with a technology determines the total revenue and profitability of that product. Moreover, the market's response to a product or class of products sends a signal to potential innovators and investors in that field; successful ventures encourage future investments in similar undertakings, while failures retard their development.

Because Medicare promises to remain the primary payer of recombinant erythropoietin for the near future, the program's payment policies will have a substantial effect on the total market for the product. Over time, Medicare's policies are likely to influence investment in endeavors perceived as similar, namely research on innovative pharmaceuticals that employ biotechnology and on other products for which Medicare would be the dominant payer.

Especially when Medicare accounts for a substantial share of the market, as it does for recombinant erythropoietin, it is advisable that policymakers at least consider the implications of payment on the industry that develops, distributes, and administers it. More controversial is the responsibility of Medicare, as opposed to other Federal programs, to encourage worthwhile innovation. Even if one accepts that the Federal Government has some responsibility to foster worthwhile innovation, it is not clear that the Medicare program, as opposed to a Federal program charged specifically with that mission, should pursue that objective if it conflicts with Medicare's role as a prudent payer of medical care for its beneficiaries.

Administrative Feasibility

The final dimension for evaluating a payment option is the administrative feasibility of implementing the measure proposed. This aspect of the analysis questions how easily Medicare's administrative structure and the country's arrangements for producing, distributing, prescribing, and dispensing drugs could incorporate the proposed change.

A complex structure to support HCFA'S administration of the Medicare program is already in place. HCFA's intermediaries administer payment for inpatient and dialysis services, and its carriers administer payment for physician services and most outpatient services. End-stage renal disease networks and peer review organizations are responsible for reviewing the quality of care provided to beneficiaries.

Most pharmaceutical products are readily available to patients and health care professionals through multiple distribution outlets across the nation. Traditionally, pharmaceutical products are shipped from the manufacturer, often through a wholesaler, to a point of distribution or administration to patients, such as physicians' offices, hospitals, pharmacies, and dialysis facilities.

Some of the potential payment options would require changes in the product and financial flows or in procedures for setting payment rates and assessing the quality of care. The extent to which these changes would pose a burden to beneficiaries, providers, distributors, manufacturers, or Government administrators represents an important aspect of an option's implications.

A further administrative consideration relates to updating payment arrangements in response to dynamic changes in the market for recombinant erythropoietin. As market conditions (e.g., the number of manufacturers, the medical conditions approved by FDA and Medicare's prominence in the market) evolve, it will be necessary for HCFA to reassess the appropriateness of the level and perhaps even the method of payment.

OPTIONS FOR MEDICARE PAYMENT

This Special Report analyzes nine options regarding Medicare payment of recombinant erythropoietin. Two general options discuss Medicare coverage of self-administered recombinant erythropoietin and Medicare payment to encourage needed research on the biologic. The other options relate to methods of paying providers or to methods of paying for the product (see table l-l). Each option is evaluated across the six dimensions described above; table 1-2 summarizes the findings for each option.

The implications of each option depend not only on its inherent qualities but also on the market circumstances under which it is applied. The market for recombinant erythropoietin is dynamic, with substantial changes likely in the next few years in the number of manufacturers and in Medicare's share of the market. In the near term it seems likely that between one and three firms will supply the market. It also seems that Medicare will, for some time, be the dominant payer for the use of this biologic.

With a single manufacturer of recombinant erythropoietin, Medicare's options for setting payment rates would be more limited. For example, using a competitive approach to determine payment rates for the product would not be feasible. Medicare would have to rely on an alternative method, such as setting a rate based on

Table l-l-Options for Congress to Address Medicare Payment Related to Recombinant erythropoietin

General Options	
Option 1:	Amend the Social Security Act to allow Medicare coverage of recombinant erythropoietin self-administered by patients.
Option 2:	Mandate the Medicare program to set different payment rates for providers who participate in approved clinical trials of recombinant erythropoietin.
Provider Payment Options	
Option 3:	Mandate the Medicare program to set a fixed rate per recombinant erythropoietin treatment.
Option 4:	Mandate the Medicare program to include payment for recombinant erythropoietin in the composite rate paid dialysis facilities and the monthly cavitation rate paid physicians for dialysis patients.
Option 5:	Mandate the Medicare program to pay for recombinant erythropoietin on the basis of customary, prevailing, and reasonable charges (CPR).
Option 6:	Mandate the Medicare program to pay for recombinant erythropoietin according to a fee schedule.
Product Payment Options	
Option 7:	Mandate the Medicare program to base payment rates for recombinant erythropoietin on manufacturer costs.
Option 8:	Mandate the Medicare program to set the payment rate at the lowest price for recombinant erythropoietin listed in the Federal Supply Schedule.
Option 9:	Mandate the Medicare program to set payment for recombinant erythropoietin through competitive bidding.

SOURCE: Office of Technology Assessment, 1990.

Table l-2-Summary of Analysis of Options for Medicare Payment for Recombinant Erythropoietin

Options	Dimensions for evaluation: Costs and efficiency	Access	Quality	Equity	Technological innovation	Administrative feasibility
GENERAL OPTIONS:						
Option 1: Coverage of self-administration	Slight to moderate increase in use end higher coats to Medicare. Decreased Medicare and beneficiary costs for patients otherwise administered product in physicians offices, depending on payment rate.	Improved access for beneficiaries on home dialysis.	Improved because of better access.	Equity Improved for home dialysis patients.	Higher revenues for manufacturers and perhaps greater incentive for innovation.	Little administrative change needed.
Option 2: Different payment for providers in clinlcal trials	Increased short-term coats to Medicare. May transfer research costs from manufacturers to Medicare. Over time, knowledge gained may reduce dose and associated expenditures.	Improved if option speeds FDA approval and access for indications not yet approved.	Improved knowledge about appropriate dose gained more quickly.	Improved for beneficiaries if knowledge gained expedites FDA approval for other indications.	Spur to innovation, if overall use rose and option was used for other technologies.	Administration of studies would increase Medicare costs moderately.
PROVIDER PAYMENT OPTIONS:						
Option3: Fixed rate par rHuEPO treatment	Incentive to reduce and to treat low-dose cases. Moderate costs for Medicare, depending on payment level. Moderate and fairly uniform out-of-pocket costs for beneficiaries.	Moderate financial access for beneficiaries.	Incentive to reduce dose below clinically appropriate levels and to treat low-dose cases.	May be moderately to highly inequitable for beneficiaries end providers.	Moderate stimulus for technological innovation.	Need to differentiate and update provider payments. Moderate to strong need for peer review to assess overuse and underuse.
Option4: Payment for rHuEPO treatment in conposite rate	Strong incentive for providers to skimp on use. Low coats for Medicare, depending on payment level. Uniform coats for beneficiaries.	High financial access for beneficiaries. Incentive for providers to deny access.'	Major incentive for providers to reduce dose below clinically appropriate level.	May be highly inequitable for beneficiaries and providers.	Reasonable threat of insufficient stimulus for technological innovation.	Need to differentiate and update provider Payments. Strong need for peer review to counter underuse.
Option5: CPR payment according to units of rHuEPO used	Strong incentive for providers to increase dose and to raise charges to Medicare. High coats to Medicare. High and variable out-of-pocket costs to beneficiaries, with strong likelihood of extremes.	Cost-sharing higher and financial access lower for high-dose patients. No incentive for providers to deny access.	Incentive for providers to increase use above clinically appropriate level.	Moderately equitable for beneficiaries and providers.	Likely to stimulate excessively innovation.	Administratively complex. Strong need for peer review to counter overuse.

Table 1-2--Summary of Analysis of congressional Options for Medicare Payment for Recombinant Erythropoietin-continud

Opt ions	Dimensions for evaluation: Costs and efficiency	Access	Quality	Equity	Technological innovation	Administrative feasibility
Option 6: Fee schedule according to units of rHuEPO used	Incentive for providers to increase dose, depending on payment rates. Moderate to high costs to Medicare, depending on payment level. Moderate and variable out-of-pocket costs to beneficiaries, with possible extremes.	Moderate financial access for beneficiaries. Little or no incentive for providers to deny access.	Incentive for providers to increase dose above clinically appropriate level, depending on payment level. Little or no incentive to reduce dose below this level.	Highly equitable for beneficiaries. Moderately equitable for providers.	Moderate stimulus for technological change.	Need to differentiate and update payments. Moderate need for peer review to counter overuse and underuse.
PRODUCT PAYMENT OPTIONS:						
option 7: Based on manufacturer costs	Risk that product price may be set too high or too low. Low price implies lower costs to Medicare and beneficiaries and cost shifting to other markets and products. High price implies higher cost to Medicare and beneficiaries and possible substitution of less effective therapies.	Low product price implies greater access for beneficiaries, and high price reduced access.	High product price may result in use below clinically appropriate levels. Low price per se should not affect use.	No implications for beneficiary or provider equity.	Low price may discourage technological innovation, while high price may provide excessive stimulus.	Calculation of an appropriate price is very difficult administratively. Logistics of implementation may be difficult.
Option 8: Buy from federal Supply Schedule	Substantial risk that product price will be set too high. Little or no risk it will be too low. High price implies high costs to Medicare and beneficiaries and potential substitution of less effective therapies.	High product price implies reduced access for beneficiaries.	High product price may result in use below clinically appropriate levels.	No implications for beneficiary and provider equity.	High product price may excessively stimulate technological innovation.	Logistics of distribution and financial flows may pose moderate administrative problems.
Option 9: Competitive bidding among manufacturers	Risk that product price will be set too low. Little or no risk it will be too high. Low prices imply low costs to Medicare and beneficiaries, but also may result in cost shifting to other markets and products or exit of new or small firms.	Low product price implies greater access for beneficiaries.	Low product price may stimulate overuse.	No implications for beneficiary and provider equity.	Low product price may discourage technological innovation.	Manufacturers/ participation uncertain. Logistics of dividing market and financial flows may pose difficult administrative problems.

KEY: rHuEPO = recombinant erythropoietin

SOURCE: Office of Technology Assessment, 1990.

its assessment of the manufacturer's costs. The presence of a single manufacturer would affect provider payment options as well. If separate providers face a monopolist manufacturer of recombinant erythropoietin, they may not have sufficient market leverage to influence the prices that they must pay for the product. As a consequence, using methods of paying providers to encourage them to more prudently purchase the biologic would be ineffective and might impair beneficiaries' access and the quality of their care. Therefore, under this market scenario, a payment option that placed less risk on the provider might be more appropriate. Also implied here is the stronger need for Medicare to apply directly its market leverage to set a payment rate for the product.

The presence of multiple manufacturers of recombinant erythropoietin would pose a contrasting market situation with different implications for payment options. Although Medicare could then apply a more competitive approach for obtaining a lower payment rate for the product, there would be less need for Medicare to use its market leverage to achieve this objective. With multiple manufacturers, provider payment methods that encouraged prudent purchasing might be capable of achieving significantly lower rates for the product. Indeed, whether it is desirable for Medicare to set a rate that it pays manufacturers for recombinant erythropoietin depends on whether any provider payment method, by itself, would be sufficiently effective across the range of dimensions to be considered.

The options considered below are not mutually exclusive. Options 1 and 2, the general options on coverage and research, could be implemented with any of the other options. Any of the options for paying providers of recombinant erythropoietin (options 3, 4, 5, and 6) could be combined with any of the options for paying for the product (options 7,8, and 9). Even within the provider options and the product options, more than one alternative could be adopted. Furthermore, these payment options are not limited to anemia associated with chronic renal failure, the only condition that Medicare currently covers; these options and the analysis of their implications apply to other conditions for which the biologic may be covered in the future.

General Options

Option 1: Amend the Social Security Act to allow Medicare coverage of recombinant erythropoietin self-administered by patients.

Title XVIII of the Social Security Act prohibits Medicare coverage of most pharmaceuticals, including recombinant erythropoietin, insulin, and most prescription drugs, that beneficiaries administer to themselves. Although these patients manage to administer dialysis treatments and related medical services at home, they must travel to their supervising dialysis facilities or physicians' offices to receive recombinant erythropoietin covered by Medicare. The time and inconvenience required may pose significant physical and financial barriers for many patients. As FDA approves and Medicare covers more indications, these restrictions will inconvenience more beneficiaries.

Under this option, Congress would amend the Social Security Act to allow Medicare to cover recombinant erythropoietin when self-administered by patients.

In regulations implementing the amendment, the Medicare program could specify the conditions under which use would be covered, such as for indications approved by FDA and for a certain level of anemia. The expanded coverage could be restricted to patients who receive dialysis at home. In fact, legislation pending in the Senate (S. 2098) and the House of Representatives (H.R. 4247) would mandate Medicare coverage for home dialysis patients.

Dialysis patients could obtain their recombinant erythropoietin and related supplies from their dialysis centers or dialysis distributors, which would both be responsible for billing Medicare. Options 3,4,5, and 6 discuss different methods that could be used to set payment rates for providers. If legislation covered self-administered recombinant erythropoietin for all FDA-approved conditions, these provider payment options could also apply to dialysis distributors and pharmacies.

Overall Medicare expenditures would increase, if this option was implemented. Easing financial and physical barriers to access typically increases use and expenditures. Physicians would be more likely to prescribe recombinant erythropoietin, especially for patients who receive dialysis at home or who have difficulty traveling. Patients' use would rise because of greater convenience and reduced costs related to travel and perhaps work loss.

The effect on program costs of beneficiaries who shift to self-administration from administration in other settings is less straightforward. Medicare pays supervising physicians who receive monthly cavitation payments for dialysis patients an additional amount for the product, but not for administering it. Medicare also pays non-supervising physicians who administer recombinant erythropoietin to dialysis patients only for the product; these physicians must bill the supervising physicians for administering the biologic. Therefore, the shift from physician to self-administration resulting from this option would not save the Medicare program any expenditures associated with administering the product.

Medicare's approved charge for the product to physicians administering recombinant erythropoietin in their offices, however, may exceed the amount that Medicare currently pays dialysis facilities ($40 per 10,000 units or fewer of the biologic). If, as specified in S.2098 and H.R. 4247, home dialysis patients were required to obtain the biologic from their supervising dialysis facilities or dialysis distributors and these providers were paid the same lower rate, Medicare's per patient expenditures could be lower. If the option applied to patients other than those on dialysis, Medicare could restrict the payment rate to the lowest paid in any setting.

Reductions in blood transfusions and other services for anemic patients would partly offset any increase in program expenses from improving beneficiaries' access to recombinant erythropoietin. One study estimated total annual savings for blood and related services at about $1,600 per transfusion-dependent patient and savings for androgens at about $900 per patient receiving them (68). Savings might also arise from reductions in untoward consequences of transfusions, such as therapy for hepatitis contracted through transfusion. In addition, transfusions may induce antibodies that lower the likelihood of successful kidney transplantation. Since

costs to Medicare of patients with successful transplants are substantially less than those remaining on dialysis, over time Medicare may reap additional savings for averted transfusions.

If Medicare restricted coverage under this option to recombinant erythropoietin obtained from a dialysis facility or distributor, out-of-pocket expenses for patients on home dialysis would be the same as those for patients receiving dialysis in facilities. Under current Medicare payment to dialysis facilities, patient out-of-pocket costs for up to 10,000 units are limited to $8 (20 percent of $40) per treatment with recombinant erythropoietin. If Medicare extended coverage under this option to indications other than dialysis and limited payment to the rate paid dialysis facilities, beneficiaries would incur the same level of out-of-pocket expenses.

Patients who self-administer the biologic would save other direct costs relating to time and travel to physicians' offices and dialysis facilities. Beneficiaries who would otherwise not have received the product would now incur the related out-of-pocket costs, but they would also gain whatever health benefits resulted from taking recombinant erythropoietin.

In response to a query from the Senate Finance Committee, the Congressional Budget Office (CBO) during the process of budget reconciliation in fall 1989 estimated the effect on Federal expenditures of covering self-administration of recombinant erythropoietin for dialysis patients (71). Assuming that half of an estimated 24,000 home dialysis patients would opt for self-administration, CBO concluded that coverage for dialysis patients would raise Federal outlays about $40 million for fiscal year 1990.[18] This estimate made no allowance for reductions in blood transfusions and other services or for patients who are currently receiving recombinant erythropoietin from a dialysis facility or physician's office. Using updated figures on home dialysis patients, CBO is re-estimating the budgetary implications of covering self-administration.

The net effect of this option on the quality of care would combine positive health benefits from alleviating anemia in newly treated beneficiaries with any negative effects associated with self-administration. How Medicare administered the benefit could greatly influence the quality of care. Medicare has already instructed its intermediaries to restrict payment to claims demonstrating hematocrit levels in a certain range and could apply those restrictions to self-administered use as well. If safety was a concern, Medicare could require that patients obtain recombinant erythropoietin from a medical provider during the induction phase and stipulate that the program would cover self-administration only after a maintenance dose is achieved. Peer review organizations (PROS) or end-stage renal disease (ESRD) networks could also assess the appropriateness of recombinant erythropoietin use, whether the drug was administered by a patient or a medical provider (see ch. 4).

The literature contains limited information on self-administration of recombinant erythropoietin. A few clinicians

18 Since coverage would have begun on Jan. 1, 1990, expenses related to only part of the fiscal year. CBO's original estimate included about $5 million additional expense for fiscal year 1990 as a result of Medicare payments associated with limits on beneficiaries' liability that were related to provisions of the Medicare Catastrophic Coverage Act of 1988 (71). Those provisions no longer apply because that Act has been repealed.

have reported that patients on home dialysis administered the biologic intravenously or subcutaneously with no unusual safety problems (see ch. 2).

To the extent that expanded coverage of recombinant erythropoietin increased the market for the product, further innovation in this and related fields would be stimulated. In addition, implementation of this option would be possible within current administrative structures. To determine payment rates for the product, Medicare could combine the techniques and information used to set payment rates for recombinant erythropoietin in other settings. As noted, under S.2098 and H.R. 4247, home-dialysis patients self-administering this biologic would be required to obtain it either from their dialysis facilities or distributors, both of which would be paid according to the same method. Applying existing procedures, PROS and ESRD networks could review the quality of care for home dialysis as well as for other patients taking recombinant erythropoietin.

Option 2: Mandate the Medicare program to set different payment rates for providers who participate in approved clinical trials of recombinant erythropoietin.

Although clinical trials have shown recombinant erythropoietin to be efficacious in correcting anemia among patients with chronic renal failure, some important clinical questions remain unanswered. Clinicians require clarification mainly about appropriate dosing regimens, both for intravenous and subcutaneous administration, and also about the safety and effectiveness of patients' self-administering the biologic. Beyond these immediate needs is information on the efficacy and safety of the product for other indications, including autologous blood transfusions and anemia associated with HIV.

Resolution of these outstanding questions could result in cost savings for the Medicare program. It is not uncommon for the effective dose of a drug eventually to be found to be substantially lower than the amount originally approved by FDA. For example, doses about half those first approved have been shown to be effective for treating acquired immunodeficiency syndrome (AIDS) with zidovudine (162). Many clinicians are now starting their dialysis patients on doses of recombinant erythropoietin that are much lower than those approved by FDA (see ch. 2).

Despite the potential advantages from improved information, providers are often reluctant to participate in clinical trials for an unapproved technology. Not only do participants incur higher costs associated with recordkeeping and protection of human subjects, but also third-party payers, such as Medicare, may not pay for the technology or associated services. In the case of recombinant erythropoietin, which FDA has approved for patients with chronic renal failure and Medicare covers for the approved indication, providers caring for patients with this condition may have no financial incentive to participate in trials.

Under this option, Congress would mandate the Medicare program to use different payment arrangements to encourage providers' participation in approved proto-

cols to refine clinical information on recombinant erythropoietin.*9 Working with clinicians, manufacturers, and FDA, Medicare could identify the specific information desired, with priority to research questions that had implications for improving patients' health and moderating Medicare's costs. These research questions could pertain to chronic renal failure or to other indications not yet approved by FDA and covered by Medicare. For treating medical conditions not approved by FDA, Medicare could make payment to providers under this option conditional on their participation in a research protocol that had been approved by the FDA.

For patients with medical conditions not approved by FDA, Medicare could offer to pay for recombinant erythropoietin on the same basis that it pays for patients with chronic renal failure. Since Medicare already covers recombinant erythropoietin for chronic renal failure, however, Medicare would have to offer a higher payment rate or a payment method more desirable to providers in order to entice their participation in clinical trials. To determine payment, Medicare could use any of the methods discussed in options 3 through 6.

The immediate effect on Medicare costs would be to increase expenditures by the amount of the demonstration plus payments for conditions not approved by FDA and whatever additional payments resulted from paying providers higher rates for patients with chronic renal failure. Over time, however, the information gathered could influence Medicare's payment rates and expenditures on recombinant erythropoietin. Although the dosing regimens that will eventually be considered appropriate are uncertain, many clinicians have been treating dialysis patients at substantially lower doses than those recommended in the labeling approved by FDA (11,17,47). Although not substantiated, it has also been suggested that subcutaneous administration requires lower and less frequent use than intravenous administration (see ch. 2). Conducting more research more quickly on the efficacy of lower doses could provide a more informed basis for setting payment rates, especially for nondialysis patients who receive the biologic through subcutaneous administration in physicians' offices. Any savings for chronic renal patients might be offset by additional expenditures for treating anemia associated with other conditions. If the research data generated by this option led to more rapid approval by FDA of recombinant erythropoietin for other conditions, Medicare might experience an earlier rise in expenditures for these additional conditions.

The net effect on Medicare expenditures would thus depend on changes in the payment rate for recombinant erythropoietin, which would reflect the level and frequency of dosing; the increase in use for beneficiaries with covered conditions; and any reductions in expenditures from correcting anemia, such as fewer blood transfusions. The effect on beneficiaries' costs would parallel changes in Medicare expenditures and depend on the specific method and level of payment that Medicare adopted.

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19 The Social Security Amendments of 1983 (Public Law 98-21) gave the Secretary of Health and Human Services the authority to pay for research and experimentation related to Medicare's prospective payment system (21 USC 1395y(1)(D)). HCFA could use this authority to pay providers who agreed to gather needed information in the context of clinical trials.

On the other hand, this option might only transfer the costs of further research from the manufacturers of recombinant erythropoietin to the Medicare program and its beneficiaries. At least three manufacturers are conducting studies pertaining to safety for chronic renal failure and to efficacy and safety for certain conditions not approved by FDA. In addition, at least one manufacturer is studying different dosage levels administered subcutaneously in predialysis patients. The manufacturers bear the full cost of this research, including the cost of the biologic; physician, testing, and other clinical services; and administrative services associated with the research. Several completed studies are also being prepared for publication. Moreover, none of the manufacturers has reported difficulty in finding researchers, clinicians, or patients to participate.

The information developed from this option might improve beneficiaries' access to recombinant erythropoietin. If data were collected and other conditions were approved by FDA more quickly, beneficiaries with these conditions would gain improved financial access to the product. Also in the direction of better financial access, any reductions in Medicare's payment rates for recombinant erythropoietin because of lower dosing regimens would reduce beneficiaries' cost-sharing.

A major advantage of this option lies in its potential to improve the quality of care received by Medicare beneficiaries. Encouraging providers to participate in research protocols could be a quick and efficient way to gather data to refine appropriate dosing regimens for intravenous and subcutaneous administration and to develop information on efficacy and safety for conditions besides chronic renal failure. The quality of beneficiaries' care would clearly benefit from better information on efficacy and safety. Clinicians would have a more valid basis on which to prescribe recombinant erythropoietin, and the Medicare program would have a more valid basis by which to evaluate appropriate use. The outstanding question, however, is whether this option would produce the desired information more quickly than the manufacturers' own testing, and if so, whether the benefits would be worth the extra cost to the Federal Government.

Developing better information on efficacy and safety more quickly could improve equity among beneficiaries. As that information led to decisions about FDA approval and Medicare coverage for other conditions, use by beneficiaries with conditions that, like chronic renal failure, would benefit from recombinant erythropoietin would also be covered. One would expect equity among providers to improve, as the new information enabled Medicare to reimburse providers for efficacious and safe uses of recombinant erythropoietin and to withhold payment for other uses.

It is not clear how the research results on balance would affect the size of the market for recombinant erythropoietin and consequent incentives for future technological innovation. Other medical conditions might receive FDA approval more quickly, but the appropriate dose might prove to be lower. More important than the market size for this particular product would be the potential for using this

mechanism to stimulate assessments of new technologies. Patient groups, clinicians, third-party payers, researchers, and manufacturers have lamented the financial obstacles to producing valid information on new technologies or on new uses of existing technologies. Using this mechanism to generate research on recombinant erythropoietin would be viewed as a test case for a possible model to develop the information needed for assessments.

Although this option would require that HCFA and its contractors establish some new procedures, much of the required administrative apparatus is already in place. FDA and Institutional Review Boards already approve in advance the design of clinical trials on human subjects for biologics seeking approval for new conditions or changes in existing labeling. HCFA could notify its carriers and intermediaries that dialysis facilities and physicians engaged in approved trials were eligible for different payment rates, and the contractors would have to institute procedures to identify these providers. A necessary element not yet in place, however, is a locus for synthesizing the research results and applying them to refine Medicare policy. Such a role would be consistent with the mandate of the recently created Agency for Health Care Policy and Research, which is charged with developing information on the effectiveness of medical technologies and, in concert with the medical community, with setting guidelines for clinical practice.

Payment to Providers

At present, dialysis facilities are the principal providers of recombinant erythropoietin to beneficiaries, a situation that reflects FDA approval and Medicare coverage only for chronic renal failure. Beneficiaries with chronic renal failure, whether in the predialysis or dialysis phase, may also receive the biologic from physicians' offices. Hospitals' provision of recombinant erythropoietin to inpatients is covered by payments that are fixed by diagnosis-related group, while provision of the biologic by health maintenance organizations (HMOs) and other competitive medical plans is covered by Medicare's monthly cavitation payment. Amgen has been selling Epogen exclusively to wholesalers, who in turn sell it to dialysis facilities, physicians' offices, and others who provide the biologic to patients. Wholesalers may also sell to other intermediate suppliers, such as pharmacies. If FDA approves recombinant erythropoietin for other conditions or if legislation extends coverage to self-administration, as described in option 1, dialysis distributors and pharmacies could also provide the product to beneficiaries. If additional manufacturers enter the U.S. market, they may choose to sell directly to other intermediate suppliers or to dialysis facilities and other providers.

Options 3, 4, 5, and 6, respectively, pertain to methods that Medicare might adopt to set rates paid to providers: payment per recombinant erythropoietin treatment; inclusion of payment for recombinant erythropoietin in the composite rate for dialysis facilities and the cavitation rate for supervising physicians; payment based on customary, prevailing, and reasonable charges; and payment according to a fee schedule. All of these options could be applied to dialysis facilities, physician providers, and dialysis distributors. The set of

feasible options for pharmacies is more limited. Option 4 does not apply to pharmacies and, although option 3 is theoretically possible, options 5 and 6 would be most practical for pharmacies. Options for hospitals, competitive medical plans, and nursing homes are not considered separately in this report.

Medicare's payment to dialysis facilities and physicians would include compensation for several components: the biologic itself; any associated supplies or services; and the physician's or other health professional's services to administer the product to a patient. If Medicare coverage was extended to self-administration, as described in option 1, payment to dialysis distributors and pharmacies would compensate for the biologic, any associated supplies or services; and any professional counseling.

In the next section, options 7, 8, and 9 discuss methods that Medicare could use to set the rate that it pays for the product itself. If the payment rate for the product is set by Medicare through an agreement with a manufacturer or manufacturers, then it would be logical to incorporate that rate into the calculation of provider payment levels. On the other hand, if Medicare does not set the rate for the product or if a manufacturer conveys price concessions directly to Medicare rather than to providers, then some alternative basis for determining provider payment levels would be" necessary. To set current payment rates for dialysis facilities, HCFA estimated providers' costs of obtaining recombinant erythropoietin based on HCFA's assessment of Amgen's costs of producing the biologic and other factors affecting the costs of providing the service, such as expected dosage levels.

Other methods are also possible for estimating providers' costs for the product as an ingredient in setting Medicare payment rates to providers. For example, Medicare might use the average wholesale price (AWP) for the product. Some Medicare carriers may be using the AWP to derive an approved charge for physicians who administer recombinant erythropoietin in their offices. Average wholesale prices, however, are usually list prices instead of the transaction prices that providers actually pay for pharmaceuticals. Although the level of Medicare payment to providers has major importance, the options presented here are structured according to methods of payment and do not consider in depth how to calculate the level of payment.

A general issue that applies to providers of recombinant erythropoietin is whether they should be required to accept assignment. Under assignment, a provider agrees to accept a beneficiary's rights to benefits, to bill the Medicare carrier instead of the patient, and to accept Medicare's payment rate as full payment for the service rendered. Current law requires providers to accept assignment for patients of dialysis facilities and dialysis distributors and for inpatients in hospitals. Furthermore, in the context of mandating transition to Medicare payment for physician services according to a fee schedule, the Omnibus Budget Reconciliation Act of 1989 (Public Law 101-239) established limits on the extent that physicians who do not accept assignment may bill beneficiaries in excess of Medicare's set rate. If pharmacies become providers in the future, Medicare could require them to accept assignment or could restrict the extent to which their charges to beneficiaries may exceed Medicare's approved rate.

Another consideration in setting provider payment rates concerns the choice between uniform and differentiated payments. Under the latter approach, payment levels would vary to reflect fundamental differences among providers. Providers of recombinant erythropoietin may serve different markets and consequently, may incur different costs of providing this service. Differentiated payments are generally more equitable, especially if they afford more even access to beneficiaries (84).

Financial incentives inherent in different payment methods influence providers' and patients' decisions about using medical services, such as recombinant erythropoietin. Payment methods that place greater financial risk on providers contain stronger incentives for them to constrain use and could result in underprovision of the product and poorer quality care. Such methods would also more strongly encourage providers to prudently purchase recombinant erythropoietin. On the other hand, payment methods that place providers at less financial risk contain stronger incentives for greater use and perhaps overprovision of the product and poorer quality care. Generally, the financial risks to providers are stronger the larger the units on which payment is based. For example, payment per treatment with recombinant erythropoietin places more financial risk on the provider than payment per unit of the product.

Levels of payment also affect use and the quality of care received by beneficiaries. For any given payment method, lower payment levels are likely to discourage use, while higher levels encourage greater use. The extent to which use varies with payment levels also depends on the incentives inherent to each payment method. For example, when the amount of payment does not vary with the volume of service, higher payment levels are less likely to result in more use than when the amount of payment does vary with volume.

As noted above, options 3, 4, 5, and 6 are not mutually exclusive; Medicare can and does use different methods to pay providers in different settings. On grounds of efficiency and equity, however, it is preferable that Medicare pay the same amount for the same service, regardless of the setting in which it is provided. Paying a higher amount in one setting, such as a physician's office, provides a financial incentive for a provider to administer the service in the most lucrative setting, regardless of where the service could be most effectively and efficiently provided. Paying different amounts for different settings may also be inequitable, if beneficiaries and providers in similar circumstances are treated differently.

Option 3: Mandate the Medicare program to set a fixed rate per recombinant erythropoietin treatment.

Medicare currently pays dialysis facilities a fixed amount of $40 per recombinant erythropoietin treatment, which increases to $70 if the dosage level exceeds 10,000 units (see ch. 4). S. 2098 and H.R. 4247 would apply this payment method to dialysis distributors for recombinant erythropoietin self-administered by home dialysis patients. This method could also be applied to physicians, but would be least practical for pharmacies.

Since under this option the amount reimbursed would not vary with the quantity of recombinant erythropoietin

administered in each treatment up to a threshold, this payment method contains a financial incentive for providers to control and even skimp on use. The fixed payment also encourages providers to make prudent purchases of the product.

Providers would also have a financial incentive to treat patients who would require especially low doses but who would gain little marginal benefit from treatment. The costs of such cases would be substantially below the payment per treatment. The consequence of this behavior would be greater numbers of beneficiaries receiving treatment and higher costs to the Medicare program. ESRD networks and PROS could monitor use for appropriateness, but PROS have had little experience in the outpatient arena.

There is some financial incentive to provide higher than the clinically appropriate dosage levels to cases just below the 10,000 unit threshold, especially if medical consequences are minor. Slight increases in dosage could nearly double the payment per treatment. Depending on the strength of this financial incentive and the proportion of cases near the threshold, costs to the Medicare program could increase significantly. Review of these claims by PROS or ESRD networks might counter overuse near the threshold.

Providers may have a financial incentive under this payment method to deny access, that is, not to administer recombinant erythropoietin when it is medically appropriate. This would not apply to patients requiring smaller dosage levels, who are likely to cost less than the payment amount. Denial of treatment might occur for patients requiring doses that are below, but closer to, the 10,000 unit threshold. Medical ethics may constrain such behavior. Although denial of access would reduce the costs of recombinant erythropoietin to the Medicare program, the costs of alternative medical services, such as blood transfusions, might increase.

If financial incentives of this option led providers to skimp on use, reduced quality of care could result, if doses fell below clinically appropriate levels. Again, this tendency would most likely depend on the seriousness of the medical consequences and the effectiveness of peer review.

It should be noted that at present, appropriate dosage levels are unclear. Dialysis facilities paid by Medicare through February 1990 averaged about 2,700 units of recombinant erythropoietin per patient per treatment, and facilities surveyed by Amgen from mid-December 1989 to mid-January 1990 averaged about 2,900 units per treatment (47,117). These rates are much lower than those recommended in the FDA-approved labeling or the 5,000-unit mean dose expected by HCFA when it set the present payment rate (5,85). These doses are also much below the mean dose that clinical trials found necessary for a response (55) (see ch. 2). Administering lower doses is consistent with the incentives of this payment method to skimp on the quantity used and to treat patients only marginally anemic. That initial doses are apparently much lower than expected, however, cannot be attributed entirely to financial incentives inherent in this payment method. Although clinical trials have shown that some patients need much greater doses of recombinant erythropoietin to respond, at present clinicians cannot determine a priori the effective dose. Consistent with usual medical practice in the face of such uncertainty,

clinicians appear to be starting with lower doses and, presumably, will raise the dose for poor responders. Over time, however, the average dose will combine the effects of newly treated patients in the induction phase, poor responders with increased doses in the induction phase, and other patients on a maintenance dose.

Under this payment method, out-of-pocket costs to most beneficiaries are fixed at $8 per treatment ($1,248 per year with 3 treatments per week). For those with doses in excess of 10,000 units, out-of-pocket costs are fixed at $14 per treatment ($2,184 per year with 3 treatments per week). Some beneficiaries may consider this distribution of out-of-pocket costs to be inequitable. For example, a beneficiary requiring very modest treatment with recombinant erythropoietin might view a $1,248 increment in out-of-pocket costs as quite unfair. This inequity would be somewhat remedied if payments to providers under this option varied to reflect differences in patient characteristics, such as weight, that affected dosing levels.

Equitable compensation of providers requires that payments be differentiated to reflect market-related differences in their costs. Some providers may treat cases who, on average, require higher dosage levels. Other providers may, because of geographic location, pay higher wages or incur higher acquisition costs for recombinant erythropoietin. Because of markups of wholesalers and other intermediate suppliers, differences in providers' acquisition costs may occur even if, as under the options in the next section, Medicare sets the price of the product with the manufacturer.[20] Under these circumstances, uniform payments might lead some providers to reduce doses below clinically appropriate levels, or to treat patients with only marginal anemia. Therefore, equity for both providers and patients and access by beneficiaries would be improved if payments were differentiated to reflect case mix and other market-related differences in cost.

This option may be less appropriate for physician providers of recombinant erythropoietin than for dialysis facilities. Because physicians treat smaller numbers of patients, they face greater financial risk from a few patients who require high doses. Since payment does not generally vary with dosage level under this option, physicians may experience considerably more incongruity between payments and costs for this service. For all providers, adjusting for patient characteristics predictive of high use is likely to prove difficult, as exemplified by problems in adjusting cavitation payment to competitive medical plans and DRG payments to hospitals. Paying pharmacies under this option would raise similar problems.

This option might affect technological innovation. If providers' incentives to lower dosage levels led to lower purchases and considerably lower revenues for manufacturers than expected, incentives to further develop this and other products

20 The wholesaler markup usually accounts for a small fraction of provider acquisition costs. According to a survey by the Office of the Inspector General conducted between November 1989 and March 1990, dialysis facilities are paying about $41 for 4,000 units of recombinant erythropoietin (85). During this period, Amgen's price to wholesalers was $10 per 1,000 units (117).

used extensively by Medicare might be dampened. The opposing financial incentive for providers to treat more low-dose cases, however, would somewhat mitigate these effect.

The administrative difficulty of this payment alternative depends on what refinements are introduced. Under the current method, payments are fairly uniform and, consequently, administratively simple. Administrative difficulty could increase substantially if payments were differentiated. Given its experience with the prospective payment system for reimbursing hospital operating expenses, the Medicare program is well aware of such difficulties. Differentiated payments, if feasible, may nevertheless be necessary to reduce the negative effects of payment methods that encourage providers to be more cost conscious. Because payment rates would be set prospectively under this option, it would also be necessary continuously to update payment levels in response to dynamic changes in the market for recombinant erythropoietin or changes in clinically appropriate dosage levels.

Option 4: Mandate the Medicare program to include payment for recombinant erythropoietin in the composite rate paid dialysis facilities and dialysis distributors and the monthly cavitation rate paid physicians for dialysis patients.

This option applies only to the payment of recombinant erythropoietin provided to dialysis patients by dialysis facilities, dialysis distributors, and physicians. Dialysis facilities and dialysis distributors are currently paid a prospective amount per dialysis treatment, which varies according to factors such as area wage costs.[21] This covers nearly all services relating to dialysis (see ch. 4).[22] Physicians treating dialysis patients are paid a monthly cavitation payment for services directly relating to this condition (34). This amount applies to patients receiving dialysis at home as well as those in facilities.

Under this alternative, the composite rate for dialysis facilities and dialysis distributors and the physician cavitation for home dialysis patients would be increased to cover the costs of recombinant erythropoietin. For dialysis facilities and dialysis distributors, the increase in the composite rate would be based on an estimate of the average amount of the product used during each dialysis session. For physicians, the increase in the cavitation amount would be based on an estimate of the average number of patients administered recombinant erythropoietin per month and the average dosage.

The principal difference between this option and option 3 is that payment would not depend on whether recombinant erythropoietin is administered. Because payment under this option depends neither on the administration of recombinant erythropoietin nor on its dosage, there are no financial incentives to treat more cases or to provide larger doses of this biologic than is clinically appropriate. This option contains stronger incentives than option 3,

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21 Consideration of the rate paid for dialysis treatment lies outside the scope of this OTA study. The Institute of Medicine Committee To Study the Medicare End Stage Renal Disease (ESRD) Program is addressing certain aspects of the rate-setting process, but is not conducting a full-scale rate-setting study (118).

22 In addition to recombinant erythropoietin, other items such as the whole bled used in transfusions are paid separately.

however, to skimp on use. Providers would also have a strong incentive to make prudent purchases of recombinant erythropoietin. The significance of this incentive is greater if Medicare does not set the price paid by providers for the product.[23] Because of the strong incentives for economy under this option, costs to the Medicare program and direct costs to beneficiaries would be kept at fixed levels. Financial access for beneficiaries might also be greatly improved because out-of-pocket extremes would not be possible.[24]

Access may be adversely affected in other ways under this alternative. Since payment is independent of treatment, providers may have a strong financial incentive to deny recombinant erythropoietin to some patients for whom its application would be clinically appropriate. Because medical consequences would be less serious, this behavior is more likely to occur with patients who are only slightly anemic. Although peer review may address this problem, inappropriate decisions regarding such patients would be difficult to detect. The financial incentives to deny access are stronger here than under the other options for provider payment. By denying access under this method, providers would save the full cost of treatment. Under option 3 they would reap only the difference between the cost and the payment per treatment.

There may also be a strong financial incentive for providers to administer doses of recombinant erythropoietin that are below clinically appropriate levels. By doing so, they would increase net revenues or reduce losses. Again, such behavior would most likely depend on the seriousness of medical consequences and the effectiveness of peer review. Under option 3 providers have the opportunity to improve net revenues by treating more low-dose patients. Since revenue does not rise with treatment under this option, there might be a greater tendency to reduce dosage levels.

Under this payment method, beneficiary out-of-pocket costs would be totally unrelated to recombinant erythropoietin use. Even patients who are not treated with this biologic would incur out-of-pocket expenses relating to its costs. For this reason, beneficiaries are likely to view this payment alternative as being far less equitable than option 3.

This payment method is likely to be even more inequitable to providers than option 3. The adequacy of compensation not only continues to vary with average dosage levels, but also varies with the proportion of dialysis cases given recombinant erythropoietin. As with option 3, inequitable compensation could also result if providers, because of different markets, incur different acquisition costs for recombinant erythropoietin, labor, or other inputs. These compensation inequities could be addressed by differentiating payments to reflect these differences among providers.

This option is even less appropriate for physician providers than option 3. Because payment is affected by neither the adminis-

23 Even if the manufacturer's price were set, providers would still have a strong incentive, under this option, to shop for the lowest wholesaler markups.

24 All dialysis patients would incur the same increase in out-of-pocket costs under this option. The increment would be 2(I percent of the increase in the composite rate or physician cavitation. The increase in out-of-pocket coats per beneficiary would also be lower under this option than under option 3, since the costs of recombinant erythropoietin would be spread across all dialysis patients rather than only those treated with this biologic.

tration of recombinant erythropoietin nor its dosage level, physicians are likely to experience even greater incongruity between revenues and costs over time. Adverse effects on patient quality and access could also be greater. The same difficulty regarding an adjustment to physician payments for relevant patient characteristics also applies here.

Given incentives for providers to skimp on use, this option could adversely affect technological innovation. If the total demand for recombinant erythropoietin fell substantially below manufacturer expectations, manufacturers could be discouraged from investing in similar therapies or in any therapies for which Medicare is a dominant payer. Because incentives to underprovide recombinant erythropoietin are stronger under this payment alternative than under option 3, the threat to technological innovation is also greater. Since higher payment levels would have little effect on use under this option and since all of its inherent incentives are for economy, there is no possibility for an excessive stimulus to technological innovation.

As with option 3, the administrative difficulty of this payment method depends on whether payment rates are differentiated to reflect fundamental differences among providers and on the extent of these refinements. Also like option 3, there is the added administrative burden of updating payment levels in response to dynamic changes in the market for recombinant erythropoietin or changes affecting appropriate dosage levels. Lastly, because of its very strong incentives for economy, it would be necessary under this option to reinforce peer review to better ensure against underprovision.

Option 5: Mandate the Medicare program to pay providers of recombinant erythropoietin on the basis of customary, prevailing, and reasonable charges (CPR).

Under this option, Medicare payment to a provider would vary according to the number of units of recombinant erythropoietin administered to a patient. The CPR method, which Medicare currently uses to pay physicians, would pay each provider an amount for the therapy that is the lesser of the actual charge, the customary charge based on the provider's previous billings, and the prevailing charge for the service by comparable other providers. Medicare could continue to permit providers who do not accept assignment to bill patients for amounts in excess of Medicare's approved charges, or Medicare could restrict providers' additional billing. As noted in option 1, physicians who receive monthly cavitation payments for supervising dialysis patients and other physicians administering the biologic to dialysis patients may charge only for the product and related supplies, not for administering it. The CPR method could also be used to reimburse dialysis facilities, dialysis distributors, and pharmacies. For these providers and for physicians administering the biologic to other than dialysis patients, payments under this option would compensate for administration or dispensing services and supplies as well as the product.

This option gives providers and patients the weakest incentives to constrain utilization and prudently purchase recombinant erythropoietin. The main difference between this method and reimbursement based on actual charges is that a ceiling is placed on the amount that Medicare will

pay. This ceiling, however, is not very effective. What is considered customary, prevailing, and reasonable is based on actual charges that with a lag determine Medicare's approved rates. Therefore, knowing that their inflated bills will increase CPR ceilings and the amounts that Medicare will pay in the future, providers have an incentive to inflate charges. The only constraints on providing and charging too much is the risk that patients will not pay their bills or, over the longer term, will seek lower cost providers.

As a type of fee-for-service payment, the CPR method gives providers a financial incentive to increase use, through higher dosage levels and treatment for greater numbers of patients, as long as the payment per unit of service exceeds the provider's unit costs. The strength of this incentive depends on the extent to which payment levels exceed costs. Overprovision can take the form of doses of recombinant erythropoietin that are in excess of clinically appropriate levels and treatment of marginal patients for whom this therapy is inappropriate. If payment just equals cost, providers experience no financial gain from exceeding clinically appropriate dosage levels or inappropriately treating patients. There may still be overprovision in an economic sense, however. The clinically optimal level of recombinant erythropoietin is not necessarily equivalent to the economically efficient level. One more unit of the biologic may have a clinical benefit, but this benefit may be insufficient to warrant the additional cost. Medicare dollars might be better used elsewhere. Thus, even if providers gain nothing financially, they may still have an incentive to overprovide. They incur no net costs from doing so and the additional costs to the beneficiary are limited by the 20-percent coinsurance rate.

Under this option, providers would have little or no incentive to shop for a lower price for recombinant erythropoietin. The weakness of this incentive is especially significant if Medicare does not set the rate at which providers may purchase the product. Because of these generally weak incentives, this option is likely to result in higher costs to both the Medicare program and beneficiaries, well above those likely under options 3, 4, and 6. Higher costs to beneficiaries mean less financial access. Financial access might also be diminished because of the greater likelihood of out-of-pocket extremes under this option.

The weakness of the CPR method is well recognized. Recent amendments to Title XVIII of the Social Security Act (Public Law 101-239) require that, after a phase-in period ending in 1996, Medicare end the current CPR method of paying for physician services and implement payment according to a fee schedule. Under the CPR method, providers would have a financial incentive to exceed clinically appropriate dosage levels and even to administer the biologic to patients for whom it is unnecessary. Given the possibility of adverse events, harmful effects from overuse are certainly possible.

The preceding discussion of provider incentives applies only to physicians and dialysis facilities that administer recombinant erythropoietin. Financial incentives to overuse pertain less to pharmacies and dialysis distributors, which do not prescribe treatment and dosage levels. The lack of incentive under this option to shop for a low price for the product, however, would still be an important factor in evaluating its appropriateness for these providers.

Because out-of-pocket costs vary with the quantity of service, this payment method may be perceived by beneficiaries

as more equitable than options 3 and 4. There may still be some inequity, however, because out-of-pocket expenses would continue to be affected by differences in charges among providers for the same service.

Since payments are related to providers' charges up to Medicare ceilings, providers incurring market-related differences in costs are far more likely to receive commensurate payments. This method is also neutral with respect to patient characteristics that affect use.

The incentives for overuse under this option may result in higher revenues and profits accruing for manufacturers and an excessive stimulus to technological innovation, especially for similar therapies for which Medicare is a dominant payer. Excessive stimulation could draw into related research and development additional resources that would have greater social value if used elsewhere. There is little possibility that this payment method would provide an inadequate stimulus for technological change.

Although Medicare carriers and fiscal intermediaries are already familiar with the workings of this payment method, the administrative burden is nonetheless substantial. Determination of the customary, prevailing, and reasonable charge is a complicated procedure that must be applied for each provider. Unlike options 3 and 4, payment differentiation occurs automatically and is irrelevant as a potentially necessary refinement .25 Also, unlike options 3 and 4, payment rates are not prospectively determined, eliminating the need to update them in response to dynamic changes in the market for recombinant erythropoietin. Lastly, although underprovision is not a problem under this option, there is still a considerable need for peer review because of the strong incentive for overprovision and the potential for reduced quality.

Option 6: Mandate the Medicare program to pay providers of recombinant erythropoietin according to a fee schedule.

Under this option Medicare would set in advance of the period in which they were to apply a schedule of fees that it would pay per unit of recombinant erythropoietin. Unit amounts would apply to the product, related supplies, and services to administer or dispense it. The fees paid could be uniform, or they could vary to reflect market-related differences in providers' cost. As noted in option 5, after a phase-in period, Medicare will pay for all physician services according to a fee schedule. Separate fee schedules could be developed for dialysis facilities, physicians, dialysis distributors, and pharmacies.

In comparison with options 3 and 4, the fee-schedule method places less financial risk on providers and patients and consequently, creates weaker incentives to constrain use and to prudently purchase recombinant erythropoietin. Like fee-for-service payment generally, if the payment rate exceeds unit cost, physicians and dialysis facilities would have a financial incentive to provide additional units of the product, especially if there are few or no adverse consequences from doing so. Although total payments would vary directly with the quantity of recombinant

25 Difficulties have arisen, however, in rationalizing payment differences between urban and rural physicians.

erythropoietin provided, a fee-schedule approach has other advantages over the CPR method. One advantage is that Medicare can control the amount paid per unit of the service, whereas Medicare passively processes providers' billings under CPR. In addition, Medicare can encourage or discourage the use of a particular service by raising or lowering payment rates.

Because of the above incentives, costs to the Medicare program and to beneficiaries would likely be higher under this option than under options 3 and 4. Higher out-of-pocket costs for beneficiaries imply less financial access. Financial access might also be less under a fee-schedule approach than under options 3 and 4, because out-of-pocket extremes are more likely. This payment method, however, would probably result in lower costs to the Medicare program and beneficiaries than the CPR discussed under option 5. If the payment is less than unit cost, providers may have a strong financial incentive both to reduce amounts of recombinant erythropoietin below clinically appropriate levels and to deny access.

Not all of the above incentives apply to pharmacies and dialysis distributors. Since pharmacies and dialysis distributors do not make decisions regarding dosage, these providers have less influence than physicians and dialysis facilities over use and cost to Medicare and its beneficiaries. In contrast to payment based on charges billed, a fee-schedule approach would encourage all providers to be prudent purchasers of the product. This situation would be beneficial to Medicare to the extent that providers' actual acquisition costs enter into the calculation of fee schedules.

Incentives to overprovide or underprovide recombinant erythropoietin would also be affected by whether payments were uniform or differentiated. Differentiated payments would be appropriate, for example, if providers faced market-related differences in wage rates and in the acquisition costs for the product. Financial gains and losses would then be smaller, and incentives to both overprovide and underprovide the service would be weaker.

A fee schedule may be the most equitable payment method from the beneficiary's perspective. Out-of-pocket costs would vary directly with and depend only on the quantity of the product used. Differentiated payments, to account for market-related differences in costs among providers, might reduce rather than improve beneficiary equity. Such adjustments would cause out-of-pocket costs to vary also with provider unit costs and might be viewed as unfair by beneficiaries.

A fee schedule is a more equitable payment method for providers than options 3 and 4. Since payments vary directly with the quantity of recombinant erythropoietin used, differences among patients would not result in uneven compensation. Uneven compensation due to market-related differences in acquisition costs for the product and other service costs, however, would still exist. The compensation imbalances under this option would be remedied if unit amounts are differentiated to reflect market-related differences in cost.

Unless payment amounts were generally inadequate and well below unit costs, this alternative should not adversely affect industry incentives for technological innovation. Utilization levels should be

sufficiently high to satisfy industry sales requirements. On the other hand, the relatively weak constraints on use inherent in this payment method could result in overuse of recombinant erythropoietin. This could give the industry an excessive stimulus for investment.

This option would be less burdensome to Medicare carriers and fiscal intermediaries than option 5, because determination of the appropriate payment for each provider would be considerably easier. Like options 3 and 4, however, this option requires the calculation of prospective rates and their periodic updating in response to dynamic changes in the market for recombinant erythropoietin. Also, like options 3 and 4, there is a potential need to differentiate these rates, which further adds to the administrative burden. Lastly, because of the potential for both overprovision and underprovision and the resulting diminutions in the quality of care relating to each, peer review is no less necessary under this option than under the other provider payment options.

Payment for the Product

This section reviews three methods that Congress could require Medicare to use to determine the rate that it will pay for the product recombinant erythropoietin. Setting a payment rate for the product, in addition to setting rates for providers, may enhance Medicare's overall ability to control the costs of this therapy. Better control of costs implies more effective use of limited Medicare resources and, therefore, more potential benefits to patients.

An important consideration in implementing payment for the product component of recombinant erythropoietin therapy is the mechanism through which a payment rate for the product would be realized by Medicare. The product flows from the manufacturer through one or more wholesalers or other intermediate suppliers before it reaches the ultimate providers. A rate agreement between Medicare and manufacturers and the consequent financial flows may or may not involve intermediate suppliers.

One possibility for handling the financial flow is that the manufacturer or manufacturers of recombinant erythropoietin pay rebates directly to Medicare. Rebates could be based on a specific amount per unit sold to Medicare providers. Volume information could be obtained from copies of claims submitted to Medicare carriers and fiscal intermediaries. If there is more than one manufacturer, specific volumes would have to be verified for each. This should not pose a problem, since each manufacturer's brand of recombinant erythropoietin could be identified from a code appearing on each claim.

A more important difficulty with this approach would arise if some manufacturers of recombinant erythropoietin did not have a rate agreement with Medicare. Since the providers of recombinant erythropoietin would not benefit from the rebates, they would have no incentive to purchase recombinant erythropoietin from Medicare-designated manufacturers. This follows from the fact that rebates paid by manufacturers to Medicare need have no direct bearing on the prices that manufacturers would charge to providers. The total cost savings to Medicare would, therefore, be more limited and would depend on the portion of Medicare providers who chose, for whatever reason, to purchase from

Medicare-designated manufacturers. As a remedy, Medicare could lower payments to providers who failed to purchase from Medicare-designated manufacturers or deny them payment altogether.

Another possibility to address this problem would be for the manufacturer to provide rebates to Medicare providers of recombinant erythropoietin rather than to the Medicare program. Providers would also be identifiable from claims. Under this alternative, providers would have a financial incentive to purchase recombinant erythropoietin produced by Medicare-designated manufacturers, because Medicare's payments to all providers would be based on the low prices negotiated with manufacturers. A major difficulty, however, is that manufacturers would be burdened with the task and cost of periodically providing rebates to thousands of dialysis facilities, physicians, dialysis distributors, and perhaps pharmacies. Alternatively, rebates could flow from the manufacturer to Medicare carriers and fiscal intermediaries which, in turn, could transfer them to providers. Medicare carriers and fiscal intermediaries already directly deal with providers on a regular basis. Since this new responsibility would raise the costs of carriers and intermediaries, it might be necessary for Medicare to raise payments to these contractors.

Option 7: Mandate the Medicare program to base payment rates for recombinant erythropoietin on manufacturer costs.

Under this approach Medicare would determine a price for recombinant erythropoietin based on a thorough review of manufacturer costs. This alternative is most applicable to a market with a single manufacturer. Although it could also be used for multiple manufacturers, the complexities involved in determining an appropriate payment rate would make it impractical relative to other alternatives.

If it wished to obtain an explicit rate agreement from the manufacturer, Medicare could use its calculated rate as a target toward which to negotiate. What actual rate emerged from negotiation, and how closely it approached the target rate, would depend on the strength of Medicare's market position relative to that of the manufacturer. Alternatively, Medicare could simply use the target rate as an input in calculating payments to providers of recombinant erythropoietin. Medicare employed a variant of this method to set the current payment rate to dialysis facilities. This latter alternative, however, would be less effective in controlling product costs, since Medicare would have no direct influence over the rates charged by manufacturers.

Calculation of a payment rate for recombinant erythropoietin on the basis of manufacturer costs poses certain difficulties. First, since manufacturers are usually developing and producing many products, it is quite difficult to allot common costs, such as basic research and development and overhead expenses, to the product in question. Common costs are costs that cannot be traced to specific products. It is typical in the pharmaceutical industry that multiple discoveries emerge from the same basic research (70). Although measurement of common costs is difficult, their allocation to specific products is more so.

Accounting methods, such as the allocation of common costs according to the projected sales volumes of the related products, are unlikely to result in appropriate payment rates (1976). In the pharmaceutical industry, the related products sold by a firm usually differ in therapeutic significance. Products emerging from the same basic research and development process are further developed and marketed, if sufficient revenues to cover incremental costs are expected. This often yields a hierarchy of related products in terms of therapeutic significance and strength of market demand (31). Larger shares of common cost are efficiently allocated to products with stronger market demands (128).[26] A product has a strong market demand if it can command a high price and if the quantity purchased is largely insensitive to price. Therefore, to allocate efficiently common costs to recombinant erythropoietin, it is necessary to estimate the strength of its market demand relative to that of related products produced by the firm or firms in question. This determination is further complicated by the fact that demand is measured over time and common costs must also be apportioned according to the expected market life of each product.

A second issue complicating this payment option concerns the determination of an appropriate profit rate for the manufacturers of recombinant erythropoietin. The average profit rate for the pharmaceutical industry may be inappropriate if common costs are allocated using accounting methods.[27] Accounting methods would allocate too small a portion of common research and development and other expenses to products with stronger market demands. Consequently, the application of the average industry profit rate to the investment base for these products would yield profits that were too low. Profit rates for individual pharmaceutical products, when calculated using an accounting allocation of common costs, have been shown to vary widely, with many being very low or negative (78). Therapeutic breakthroughs, such as recombinant erythropoietin, generally have high accounting profits. If common costs were appropriately allocated among related products, profit rates would be more uniform.

It has been argued that large accounting profits on successful products are necessary to offset accounting losses on unsuccessful ones, and that only through these can firms earn an adequate overall rate of return (169). Therefore, if accounting methods are used to allocate common costs, and they may be the only practical methods to use, it maybe more appropriate to apply to recombinant erythropoietin the average profit rate for significant therapeutic breakthroughs rather than the average rate for the industry. Actual profit rates, whether for specific classes of products or for the pharmaceutical industry as a whole, are appropriate for the rate calculation in this option only if competition in the industry is sufficient to keep overall profits at reasonable levels.

26 The efficient allocation of common costs is essentially equivalent to pricing according to what the market will bear. Therefore, pharmaceutical firms automatically achieve this objective in their pursuit of profits. Although this may lead to product prices that are efficient relative to one another, absolute prices may still result in excessive profits if firms possess considerable market power overall.

27 Accounting methods would tend to allocate common costs on the basis of the projected volumes for each product and would not take into account the product's value to consumers and their sensitivity to price.

Despite considerable research (3,32,36, 39,1 15,169), the degree of competition in the pharmaceutical industry is still unclear. Consequently, it is difficult to know whether industry profit rates are acceptable for calculating a product rate under this option. An analysis of the average profit rate for the industry might reveal something about the degree of competition. Interindustry comparisons of profit rates are often used in such evaluations. Extreme caution, however, should be applied in making comparisons. Differences could be justified by differences in risk and the timing of returns. Also, profit rates in the pharmaceutical industry should be carefully interpreted and compared with those in other industries, because they are very sensitive to accounting practices and other assumptions made in their calculation (9,22,30,135).

A third complication affecting this payment option concerns inefficient uses of resources. In addition to price competition, some pharmaceutical firms may compete in other ways that are wasteful. Such behavior is possible in an industry that is not purely competitive but is characterized by the imperfect competition associated with brand names and product differentiation. Inefficiency arises if products are marketable at prices that cover incremental costs, only because of "persuasive" promotion. Persuasive promotion is distinct from "informative" promotion, which serves the important function of educating potential users regarding the merits and possible side effects of a product. Persuasive promotion goes beyond conveying to potential buyers the information necessary for making rational purchasing decisions (88) and attempts to encourage purchase by distorting information or by offering benefits unrelated to the product's price. In addition to encouraging imprudent purchases, expenditures on persuasive promotion are in themselves wasteful of resources. Studies have shown persuasive promotion to be a significant factor in the pharmaceutical industry (73,74). To the extent that this behavior applies to the manufacturers of recombinant erythropoietin, price determinations under this option might limit allowance for promotion and other expenditures relating to products marketed in this manner.

The implications of this option depend on whether Medicare succeeded in calculating a payment rate that reflected the costs of efficient production, including a normal profit. Whether this result would occur, however, is not predictable. If the calculated rate was substantially higher or lower than the rate that reflected efficient production, a number of problems could arise. A high rate would mean fewer benefits per dollar allocated to recombinant erythropoietin and higher costs to the Medicare program. Depending on how Medicare set payment rates for providers, it might also result in 1) the substitution of less effective therapies, such as blood transfusions, with perhaps deleterious effects on patients' health, 2) higher out-of-pocket costs for beneficiaries and consequently, less financial access and lower quality of care, and 3) an excessive stimulus to the pharmaceutical industry for technological innovation. A low rate might be harmful, because it could also distort the selection of therapies and provide an inadequate stimulus for technological innovation. In addition, a low rate could cause the manufacturer of recombinant erythro-

poietin to shift costs to other markets or products, depending on how these prices were determined.

A principal drawback of this option is the difficulty of calculating a payment rate that compensates fairly and encourages the efficient use of resources. Although this consideration is crucial, it also adds significantly to administrative difficulty. Other factors contributing to the administrative costs of this option include the staff resources needed to obtain and update information for periodically recalculating the payment rate for the product. Recalculations would be needed to reflect changes in product volumes, input costs, and other factors that in turn affect the costs of producing and distributing the biologic.

Option 8: Mandate the Medicare program to set the payment rate at the lowest price for recombinant erythropoietin listed in the Federal Supply Schedule.

The Federal Supply Schedule (FSS) is a catalog of single- and multiple-source products that are available from various manufacturers to the health care facilities of certain agencies of the Federal Government, such as the Department of Veterans Affairs (VA), the Department of Defense, the Public Health Service, and the Centers for Disease Control. The FSS is distinct from products directly purchased by the VA and distributed to facilities through its depot system. Administrative responsibility for the FSS has been delegated by the General Services Administration to the Department of Veterans Affairs Marketing Center (107,120).

The FSS represents prices negotiated with manufacturers.[28] Federal Government medical centers may buy products at FSS prices directly from these manufacturers. The prices listed on the supply schedule are less than or equal to the lowest prices charged to the same class of trade in non-government transactions. Each manufacturer wishing to list on the FSS must provide the VA Marketing Center with complete and confidential information on the prices charged to other customers. The final price is arrived at after negotiation between the VA Marketing Center and the manufacturer (107,120).

Federal Government medical centers are ordinarily required to purchase the lowest priced item on the FSS that meets their needs. Product orders are placed directly with and are shipped from the manufacturer. The Federal Government does not ordinarily guarantee that any specific volume of the product will be purchased by Government medical centers from the manufacturers listing in the FSS. In addition, facilities may purchase from suppliers not on the FSS if the prices charged by these are lower than the lowest priced products on the FSS (107,120).

As a payment option, Medicare dialysis facilities and perhaps other providers of recombinant erythropoietin could be allowed to purchase this product at the price listed in the FSS. This approach, of course, assumes that at least one recom-

28 FSS prices now include delivery to Government medical centers. A different arrangement could be negotiated for recombinant erythropoietin and Medicare dialysis facilities.

binant erythropoietin product is listed.[29] The FSS approach has the advantage of applying the weight of the Federal Government's purchasing power. In this respect it is superior to option 7, in which Medicare would negotiate independently with the manufacturer or manufacturers of recombinant erythropoietin. Nevertheless, the FSS approach may still be a weak method for obtaining the best possible prices from manufacturers.

There seems to be no strong incentive for manufacturers of recombinant erythropoietin either to participate in the FSS or to offer the lowest prices that they will accept, if they do choose to participate. Since manufacturers can later reduce prices and since the Government ordinarily makes no sales commitments to low bidders, the best strategy for a manufacturer may be to offer an FSS price that is considerably higher than the lowest price that the company would accept. High FSS prices give manufacturers the option of either sticking to those prices or selectively offering prices lower than the FSS ones, if competitive pressures warrant. At present, the Government, chiefly through Medicare beneficiaries, accounts for most of the U.S. market for recombinant erythropoietin (see ch. 3). It does not seem that, under such circumstances, a manufacturer would list in the FSS at a significantly discounted price, unless compelled to do so by the threat of lost sales. This situation may change if the non-Medicare market expands.

In any case, there may be some advantages to manufacturers of recombinant erythropoietin from appearing on the FSS as relatively low-priced sellers. Because of wide exposure, it could significantly reduce the need for direct marketing. It could also build good will with both the Government and providers.

Another difficulty that applies specifically to recombinant erythropoietin is the limited information on prices paid by comparable non-government purchasers. For the only indication that the FDA has approved to date, chronic renal failure, the Federal Government is by far the dominant domestic payer. Also, because of difficulties relating to the translation of foreign currencies into U.S. dollars and because of foreign government regulation of prices for recombinant erythropoietin, foreign prices may not be appropriate for comparison (see ch. 4 for foreign prices of recombinant erythropoietin adjusted for purchasing power parities among foreign currencies). Therefore, adequate reference prices from which to negotiate Government price concessions may not be available. This limitation, however, should be eased as more indications for recombinant erythropoietin receive FDA approval.

There appears to be little or no possibility under this option for FSS prices for recombinant erythropoietin to be too low. As argued, however, incentives are such that they could be well above the lowest prices that manufacturers would accept.[30]

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29 Effective Jan. 1, 1990, Amgen listed recombinant erythropoietin on the FSS. The Federal Government was given a 2-percent discount off Amgen's list price of $20 per 2,000-unit vial, $40 per 4,000-unit vial, and $100 per 10,000-unit vial (117,139).

30 Pharmaceuticals listed in the FSS average 41 percent below the average wholesale price (AWP) for single-source products and 67 percent for multiple source ones (138). The AWP is an inappropriate benchmark, however, since it is a list price and is not usually charged to any purchaser. Moreover, recombinant erythropoietin is a recent therapeutic breakthrough, and the above discounts may not apply to such products.

As discussed in option 7, higher prices mean fewer benefits per dollar allocated to recombinant erythropoietin and higher costs to the Medicare program and beneficiaries. Higher beneficiary costs may reduce access to this product and result in lower quality care. High prices may also provide a socially inappropriate stimulus to technological change.

Although this option has the advantage of the FSS' already being in place, it may still pose some administrative difficulties. These difficulties apply less to dialysis facilities and distributors than to other providers of recombinant erythropoietin. The Government facilities currently purchasing from the FSS are relatively large and few in number. Therefore, the logistics of distributing products to these facilities at FSS prices are manageable. Also, because these facilities serve government-related personnel only, there is little risk to manufacturers that products purchased at FSS prices will be used for non-government purposes. If additional indications for recombinant erythropoietin are approved and Medicare coverage is broadened, very large numbers of physicians and retail pharmacies could be involved. The distribution logistics implied may be far more complicated than those for existing FSS purchases. In addition, the above providers of recombinant erythropoietin serve other than government-related beneficiaries. This could significantly increase the risk to manufacturers that recombinant erythropoietin purchased at FSS prices would be used for unintended purposes.

Both of the above problems, however, would be considerably reduced if the FSS approach were applied only to dialysis facilities and distributors. In 1989, there were about 1,800 dialysis facilities that served primarily beneficiaries of government programs (see ch. 4) (156).

Option 9: Mandate the Medicare Program to set payment rates for recombinant erythropoietin through competitive bidding.

Under this option prices for recombinant erythropoietin would be obtained through a bidding process established by Medicare. Although competitive bidding could take place with as few as two suppliers, its effectiveness generally increases with the number of bidders. Medicare could set the rules and payoffs of the bidding process, and these would influence how closely price offerings approach the lowest price that each manufacturer would accept. A crucial requirement of the competitive bidding approach is that awards be clear and irrevocable. This means that Medicare must guarantee, through contract, recombinant erythropoietin volumes to the winning bidder or bidders. Otherwise, as with the FSS, suppliers would have little incentive to offer their lowest acceptable prices.

Two basic bidding approaches have been identified and evaluated (95). Under one approach, manufacturers of recombinant erythropoietin would openly quote prices to Medicare with the freedom of making reductions in response to each other's bids. Since bidders are unlikely initially to know the lowest acceptable prices of their rivals, prices would be lowered through successive rounds of bidding. Each bidder, for fear of losing, would have an incentive to gravitate toward its lowest acceptable price, and each bidder, except the winner, would eventually be compelled

to reveal this price. The winner would have to bid only slightly below the previous bid in order to win. Therefore, the timing bid could exceed the lowest price that the winner was willing to accept by some unknown amount.

Under a second approach, manufacturers of recombinant erythropoietin would offer sealed bids to Medicare. The principal difference here is that manufacturers would not be able to adjust offers in response to the observed bids of rivals. If bidders have little or no information regarding each other's lowest acceptable prices, bids would reflect each manufacturer's tradeoff between the probability of winning and winning with a price that, in retrospect, is unnecessarily low. The more severe the consequences of losing Medicare sales, the closer will bids be to each manufacturer's lowest acceptable price.

Without additional information, it is unclear which bidding approach would be more advantageous to Medicare. Open bidding would yield a price slightly below the lowest acceptable price of the second-lowest bidder. Depending on the financial consequences faced by manufacturers, sealed bidding would yield a price that is either higher or lower than the above price. Sealed bidding would be more advantageous to Medicare if the manufacturers of recombinant erythropoietin would incur major financial losses from not winning a contract. Manufacturers would probably be very averse to losing Medicare sales if Medicare accounted for the dominant share of the market for recombinant erythropoietin and if this biologic accounted for a large portion of each firm's total sales. Alternatively, if the Medicare market was of considerably less importance, manufacturers' aversion to losing Medicare sales might also be less. Under these circumstances, open bidding might be superior. Under either approach, a larger number of bidders (manufacturers of recombinant erythropoietin) would be advantageous to Medicare, because it is more likely to result in the winning bid's being closer to the winner's lowest acceptable price.[31]

The issue of single or multiple winners should also be considered. Multiple winners are possible even if there are only two manufacturers of recombinant erythropoietin. Although the price would be set at the lowest bid, guaranteed sales to the lowest bidder should be significantly greater. This approach is necessary to maintain manufacturers' incentives to reveal their lowest acceptable prices and to discourage collusive behavior. Although a single winner may provide maximum incentives, this approach could be very harmful to losers, the market for recombinant erythropoietin, and the industry. If Medicare accounts for all or nearly all of the market, exclusion of losers might result in their permanent elimination. This would make the market less competitive and could result in higher prices for recombinant erythropoietin in the long run.

A possible disadvantage of multiple winners pertains to the logistics of dividing the Medicare market among manufac-

31 For open bidding, the difference between the winner's lowest acceptable price and that of the preceding bidder would most likely diminish as the number of bidders increased. For sealed bidding, a larger number of bidders would reduce the probability that each would win with any given bid. This should induce manufacturers to lower their bids, putting them closer to their lowest acceptable prices.

turers. A relatively simple approach would be geographically to divide the Medicare market for recombinant erythropoietin. The lowest bidder, for example, could be guaranteed the largest portion (percentage of sales) of the Medicare market and the freedom to choose which geographic areas would be included in this share. The remainder of the Medicare market could be divided in a similar manner, with the second-lowest bidder getting the next largest share, and so forth. Medicare would require all participating manufacturers to sell the biologic at the winning price bid. To receive payment, Medicare could require providers in each geographic area to purchase the brand of recombinant erythropoietin that Medicare designated for that area.

Difficulties might arise, however, if one organization had dialysis facilities in areas designated for different areas. Such an organization might be faced with obtaining recombinant erythropoietin from more than one source, a situation that could reduce the organization's ability to negotiate a lower price from suppliers. Another complication would arise if the brands of recombinant erythropoietin are not therapeutically equivalent and if these differences are protected by patent. This implies that for some patients, the different brands would not be interchangeable. In that case, totally excluding a brand from a geographic area would not be feasible. As a solution, physicians could be required to justify a specific brand for those patients for whom substitution would be clinically inappropriate e. Manufacturers being awarded geographic contracts should be allowed to produce and distribute all versions of the product within legal limits.

As long as manufacturers of recombinant erythropoietin do not refuse to participate in a Medicare bidding process, this option would appear to be an effective method for obtaining competitive prices. There is little reason to believe that resulting prices would be too high. It is possible, however, that prices could be too low. For example, if Medicare's market position was very strong and a single timer was specified, manufacturers might make bids that were below the costs of efficient resource use.

Any price that would at least cover the incremental costs of producing and distributing recombinant erythropoietin could emerge under this option. Such a price, however, might contribute little or nothing to common costs, that is, the costs of resources that are used by more than one product. As argued, this is inefficient for a product, such as recombinant erythropoietin, that would face a strong demand under normal market circumstances. Medicare can prevent manufacturers from bidding prices that are too low by reducing the risks from not doing so. Risks to manufacturers would be reduced if multiple awards were made and if the differences among awards were smaller.

Prices that are too low can provide inadequate incentives for technological innovation, both for the class of products in which recombinant erythropoietin is included and for all pharmaceuticals for which Medicare is a dominant payer. Low prices may also cause manufacturers of recombinant erythropoietin to shift costs to other markets and products.

Competitive bidding has been used by State and local governments to set payment

rates for health care services, but the results have been mixed (96). Although public and private organizations that deliver health care have obtained certain services or products through competitive bidding, the results of similar attempts by governments acting as third-party payers have been disappointing. Despite the potential, it is not clear that these arrangements have resulted in lower prices or lower expenditures for the programs.

In some cases, manufacturers or suppliers have refused to participate. For example, brand-name manufacturers did not offer bids in response to a solicitation from the Kansas Medicaid program regarding pharmaceutical products (9a). Compared with this situation, however, the Medicare program represents a different market with different incentives for manufacturers. With the Kansas Medicaid program, manufacturers had to weigh the possibility of lost sales to that program against the possibility of much larger revenue losses if price concessions had to be shared with other State Medicaid programs. Given Medicare's current predominance as a payer of recombinant erythropoietin therapy, the possibility of lost payments from Medicare would most likely outweigh negative effects on other markets.

Quality problems that have plagued some other competitive bidding programs would be less likely to apply to recombinant erythropoietin under Medicare. Past difficulties seemed to have stemmed in large part from an inability to define precisely the service. Recombinant erythropoietin, however, is a more specific product whose quality is already controlled by FDA requirements.

The administrative responsibilities of conducting a competitive bidding process, monitoring the contracts, and distributing rebates from manufacturers would entail additional costs for HCFA. Also unique to this option are administrative difficulties regarding the division of the Medicare market, if multiple winners are specified. Medicare has not previously negotiated a price for an intermediate product that is used by medical providers rendering services to beneficiaries. In many cases, a demonstration project within a limited geographical area enables HCFA to evaluate the feasibility of an innovation, but such a demonstration project would not provide a fair test of this option. If the option applied only to a given region, manufacturers would have less incentive to participate and to tender low bids. It would be more reasonable initially to implement the option for dialysis facilities, which currently treat most of the beneficiaries receiving recombinant erythropoietin. Administrative procedures regarding rebates, for example, would be more manageable for the smaller number of dialysis facilities than if physicians' offices were also included. If successful, the option could subsequently be expanded to physicians.

CONCLUSION

Selecting payment options for Medicare payment of recombinant erythropoietin requires balancing desirable and undesirable implications. The most important tradeoffs relate to improving access to and quality of care for beneficiaries vs. constraining costs to Medicare and its beneficiaries.

Of all the options analyzed, option 1 (extending Medicare coverage to self-administration of the biologic) would most improve access to care, especially for home

dialysis patients. Such an extension of coverage would reduce beneficiaries' expenses, but raise those of the Medicare program. Option 2 (setting payment rates to encourage providers to engage in further research) has the potential to improve substantially the quality of care that beneficiaries receive over time. However, this option might merely transfer costs from manufacturers to the Medicare program.

Among options for paying providers of the biologic, option 4 (including payment for recombinant erythropoietin in the composite rate paid to dialysis facilities and in the cavitation rate paid physicians for dialysis patients) has the greatest potential to constrain Medicare expenditures and beneficiaries' out-of-pocket expenses. This option, however, also contains the strongest incentive for providers to skimp on use, which could damage the quality of care that beneficiaries receive. Along with option 4, option 5 (basing Medicare payment on customary, prevailing, and reasonable charges (CPR)) has the worst implications for the quality of care, but from a different direction. The CPR method threatens the quality of care by rewarding overuse of the biologic and at the same time has the greatest potential to fuel inflation in Medicare expenditures and beneficiaries' cost-sharing. Option 3 (paying a fixed rate per recombinant erythropoietin treatment), the present method, is likely to produce moderate expenditures for Medicare and its beneficiaries. This option moderately rewards providers who skimp on dosage, a practice that is subject to quality review. Option 6 (paying according to a fee schedule) may contain moderate incentives encouraging use, with implications for expenditures and the quality of care. These drawbacks can be addressed, however, by judiciously setting payment levels and by monitoring use. Adoption of this option would apply to recombinant erythropoietin the same payment method that the Omnibus Budget Reconciliation Act of 1989 recently mandated for Medicare payment of physician services generally.

Under present policy, Medicare varies the level and method of payment for recombinant erythropoietin therapy according to the setting in which it is provided. Equity among beneficiaries and providers and incentives for efficient use of medical services would argue for paying the same amount for the same service, regardless of where it was provided.

If Congress adopted an option for paying for the product itself, the resulting payment rate for the product could be incorporated into the level of payment for providers. Of the product payment options, option 9 (setting payment for the product through competitive bidding) has the potential in the short term to result in the lowest price for Medicare and the lowest expenditures for the program and its beneficiaries. Less clear, however, are its feasibility and the likely effects over time on the viability of companies heavily dependent on Medicare revenue and hence on the competitiveness of the industry.

The viability and advisability of the particular options for product payment must be considered within the dynamic context of the market for recombinant erythropoietin. With only one manufacturer about to enter the market, HCFA used option 7 (basing product payment on manufacturer costs) to set current payment rates for providers, but the impracticality of this option

increases with the number of manufacturers. Given Medicare's predominant position as a payer of recombinant erythropoietin therapy, it is unlikely that, under option 8 (using the Federal Supply Schedule), manufacturers would give substantial price concessions. To be viable, option 9, which calls for competitive bidding, requires at least two manufacturers. Indeed, any contractual agreement between Medicare and a manufacturer would have to take into account the stability of market conditions and the effect on the long-term competitiveness of the industry. If additional manufacturers were poised to enter the market, for example, Medicare would probably benefit from delaying its contracts or limiting them to a short period.

Whatever payment options are adopted, HCFA will have to be able to exercise flexibility in monitoring and responding to changing market conditions. In this dynamic market, the number of manufacturers, FDA-approved medical indications for use, and, eventually, Medicare's predominance are likely to evolve over time. The appropriate level and perhaps even the method of payment may well change with market conditions. HCFA's responsiveness to continuing changes promises to influence the quality of care, Medicare and beneficiary expenditures, and the positions of manufacturers and providers.

INTRODUCTION

The purpose of this chapter is to summarize and analyze the clinical literature on the safety and efficacy of recombinant erythropoietin. First, the etiology of and treatment method for anemia associated with chronic renal failure are discussed. Next, the efficacy of recombinant erythropoietin is analyzed with information from clinical trials in chronic renal failure patients. Issues discussed include the effect of recombinant erythropoietin on physiologic parameters, such as hematocrit level, and on the quality of life. This section also examines the efficacy of various doses and routes of administration of the product, including intravenous and subcutaneous routes. Other anemic conditions in which recombinant erythropoietin may be clinically useful are reviewed. The final section considers safety issues related to the use of recombinant erythropoietin, including adverse reactions.

TREATMENT FOR ANEMIA ASSOCIATED WITH CHRONIC RENAL FAILURE

Anemia is characterized by a significant reduction in red blood cell mass and a corresponding decrease in the oxygen-carrying capacity of the blood (23). Red blood cells are the cellular components of blood responsible for the transport of oxygen to body organs and tissues. Sustained lack of tissue oxygenation results in hypoxia, which is characterized by fatigue, weakness, lethargy, decreased ability to exercise, difficulty breathing, loss of appetite, and a overall decreased sense of well-being. Severely anemic patients may have these symptoms at rest and be unable to tolerate any level of exercise. Some may develop heart failure or transient loss of consciousness, while individuals with mild cases of anemia may or may not exhibit these symptoms.

In addition, due to decreased blood flow to the skin, anemic patients are often sensitive to cold and have pale skin color. Anemic males may complain of impotence, while anemic females may have irregular menstrual cycles. Other signs of anemia are dizziness due to lack of oxygen to the brain, irritability, and difficulty in sleep and concentration (23).

One criterion for the diagnosis of anemia is the hematocrit level, which is the volume of red blood cells expressed as a percentage of total blood volume. The average hematocrit level in men is 42-53 percent, and in women 37-47 percent (12).

There are many causes of anemia: loss of red blood cells, decreased production of red blood cells, and increased destruction of red blood cells (hemolytic anemias). Bleeding from surgery or trauma are examples of anemia associated with red blood cell loss. In hemolytic anemias, red blood cells are rapidly destroyed by the body and have a short survival time. Decreased production of red blood cells may occur through lack of iron, vitamins, or naturally occurring hormones, such as erythropoietin.

When the body detects hypoxia, erythropoietin, a hormone produced primarily by the kidneys, is released into the blood stream.[1] This hormone stimulates the release of red blood cell precursor cells from the bone marrow into the blood stream. These precursor cells work with iron stores in the body, assuming these are sufficient, to develop into mature red blood cells, and the hypoxia is corrected (23).

Successful treatment for anemia depends on the underlying causes of the condition in the patient. One method for treating anemia caused by iron deficiency is through the administration of supplemental iron. Other anemias, such as those due to insufficient bone marrow stores of precursor cells, or insufficient endogenous erythropoietin, are usually irreversible and have been historically treated with other measures, primarily periodic blood transfusions.

[1] About 90 percent of endogenous erythropoietin is produced by the kidneys, and 10 percent is produced by the liver (63).

Box 2-A--Dialysis Treatment Methods

The two major forms of treatment for individuals with chronic renal failure are kidney transplantation and some form of dialysis. The term dialysis refers to any process in which the components of a liquid or solution are separated on the basis of the selective movement of different kinds of molecules through a semipermeable membrane. The movement of the molecules through the membrane is caused by the differences in concentrations of salts and toxins in the blood and in the dialysate that is used to cleanse the blood (27).

The different methods of dialysis and the frequency of their use in the U.S. dialysis population are listed in table 2-1. The most commonly used form of dialysis is hemodialysis, in which a machine pumps blood from the patient's body and returns it through an external blood loop. Waste products and other molecules are passed through a semi-permeable membrane, so that blood can be faltered and cleaned. Hemodialysis patients usually require a total of 13 to 15 hours of dialysis weekly, for sessions of about 3.5-4 hours each (27). In 1988, approximately 85 percent of all dialysis patients, both Medicare and non-Medicare, used this method of dialysis (156).

Table 2-l--Dialysis Treatment Methods Used in the United States by Medicare[a] and Non-Medicare[b] Patients, December 31, 1988

Hemodialysis		
In-unit	86,250	(81.7%)
Home	3,197	(3.0%)
Subtotal	89,447	(84.7%)
Peritoneal		
In-unit intermittent	365	(0.4%)
Home intermittent	326	(0.3%)
Home CAPD	13,318	(13.0%)
Home CCPD	1,922	(2.0%)
Subtotal	15,931	(15.0%)
Self-Training		
Subtotal	580	(0.3%)
Total U.S. dialysis population	105,958	(loo%)

a As of Dec. 31, 1988, 91,820 dialysis patients were covered by Medicare and 6,371 had Medicare coverage pending. The percentage distribution of dialysis patients by dialysis method is for the total U.S. dialysis
b population.
Patients in the non-Medicare category may include those who are covered by the Veterans Administration, private insurance (including those who have employer group health insurance coverage for the first year of ESRD, with Medicare's becoming the primary insurer thereafter), and Medicaid; foreign nationals; and individuals with no coverage.

KEY: CAPD = continuous ambulatory peritoneal dialysis; CCPD = continuous cycling peritoneal dialysis.

SOURCES: Sagel, 1990 (124); US DHHS, HCFA, 1989 (156).

Although most patients receive hemodialysis treatments in dialysis facilities, some have been trained to perform hemodialysis at home. Home dialysis requires self-reliance, but permits freedom from a facility's dialysis schedules. Because of the possibility of medical complications resulting from hemodialysis, patients with severe medical problems are usually not considered candidates for home hemodialysis (27). Only 4 percent of all dialysis patients are on home hemodialysis (157).

Box 2-A--Dialysis Treatment Methods--Continued

In the other major dialysis method, peritoneal dialysis, a dialysate or cleansing fluid is introduced into a permanent catheter that has been inserted into the abdomen or peritoneal cavity (146). After remaining in the cavity for a period of time, the dialysate is drained out and discarded. Approximately 15 percent of patients utilize some form of peritoneal dialysis (157).

There are three commonly used forms of peritoneal dialysis. Intermittent peritoneal dialysis involves the use of a machine to deliver sterile dialysate to the patient's peritoneal cavity and, after the prescribed time, to remove the dialysate. This technique, which can be performed both in the facility and at home, is usually carried out for 10 to 12 hours 3 times weekly (146). As the patient's renal function declines, longer treatments are needed with this method.

Continuous ambulatory peritoneal dialysis (CAPD) involves continuous, manual exchange of dialysate, roughly every 4 to 6 hours. CAPD requires no machine, and the patient can usually perform the task without additional assistance. In CAPD, the patient empties a 2-liter bag of dialysate fluid into the peritoneal cavity and then proceeds with usual activities for the next 4 to 8 hours or overnight (146). At the end of the cleansing time, the dialysate is drained. The process is repeated 3 to 5 times daily, 7 days a week. The patient must be cautious to use sterile technique at all times. Due to the number of bag changes, the major risk to the patient with this form of dialysis is peritonitis, an infection of the lining surrounding the abdomen.

Continuous cycling peritoneal dialysis (CCPD) is a combination of the intermittent and CAPD methods. CCPD uses a machine to warm and cycle the dialysate in and out of the peritoneal cavity automatically about every 4 hours as the patient sleeps. The dialysate is instilled in the cavity in the morning and remains there until connection to the machine in the evening. Although still small in total number of patients, CCPD is the fastest growing method of dialysis, increasing 26 percent in use during the period 1982-1987. This method does not predispose the patient to peritonitis as much as CAPD, due to the fewer number of connection changes to the dialysis machine (146). Both CAPD and CCPD are home methods of peritoneal dialysis.

The choice of patient dialysis treatment and setting depends on the patient's medical condition, ability to participate in self-care, the level of support from friends and family at home, and treatment preferences (16). Home dialysis can give those patients needing dialysis a certain measure of independence and may reduce the cost of in-unit personnel needed for dialysis. Approximately 18 percent of all dialysis patients utilize some form of home dialysis (157). Home hemodialysis training takes from 3 weeks to 3 months, and home peritoneal dialysis training takes from 1 to 2 weeks. A profile of home dialysis patients is provided in table 2-2.

Table 2-2--Home Dialysis Treatment Methods Used in the United States by Medicare and Non-Medicare Patients, December 31, 1988

Dialysis method	Number of patients	Percent of home dialysis patients
Hemodialysis	3,197	17
Peritoneal	15,566	83
Intermittent	326	2
CAPD	13,318	71
CCPD	1,922	10
Total	18,763	100

KEY: CAPD = continuous ambulatory peritoneal dialysis; CCPD = continuous cycling peritoneal dialysis.
SOURCE: US DHHS, HCFA, 1989 (156).

Anemia is frequently associated with chronic renal failure, a progressive condition that results in permanent and irreversible destruction of the kidneys. Chronic renal failure progresses from a predialysis phase, where the kidneys continue to function but at a reduced rate, to a later phase, where there is little or no kidney function and continuous dialysis is needed to remove waste products from the blood stream (21) (see box 2-A and tables 2-1 and 2-2).

In most chronic renal failure patients, the survival time of red blood cells is only slightly decreased, and anemia results primarily from underproduction of red blood cells. This is due to insufficient production of endogenous erythropoietin by failing kidneys (21). The anemic condition worsens as kidney function declines?

The prevalence of anemia in dialysis patients is substantial. Among approximately 13,000 dialysis patients tested by National Medical Care (NMC)[3] in 1989, for example, approximately 93 percent had a hematocrit level less than 35 percent, 74 percent had a hematocrit less than 30 percent, and 70 percent had a hematocrit between 20-29 percent (see table 2-3). For predialysis patients, estimates of the prevalence of anemia vary widely, from 10-44 percent (see ch 3. and table 3-5). The symptoms of anemia associated with predialysis are, in general, not as debilitating as the symptoms of anemia associated with later-stage chronic renal failure (123).

Until recently, the treatment of anemia associated with chronic renal failure had been limited to the use of blood transfusions, androgen therapy, and administration of supplemental iron (57).

2Other factors associated with the anemia of chronic renal failure include unavoidable blood loss during the dialysis procedure, decreased red blood cell survival time, and iron deficiency (80).

3 NMC is the nation's largest chain of dialysis centers (11).

Table 2-3-Distribution of Hematocrit Levels of Dialysis Patients, by Age, January 1988[a]

	Percentage of patients with specified hematocrit level						
Age	< 1 4	15-19	20-24	25-29	30-34	≥35	Cumulative percent by age[b]
0-14	0.00	0.02	0.07	0.11	0.02	0.02	0.23
15-24	0.00	0.32	1.00	0.57	0.14	0,05	2.30
25-34	0.05	0.63	2.92	2.73	0.99	0.43	10.05
354..	0.02	0.48	4.06	4.68	2.07	o.%	22.38
45-54	0.02	0.50	4.60	6.06	3.06	1.36	37.97
55-64	0.02	0.75	6.97	10.01	4.94	2.03	62.69
65-74	0.00	0.41	6.51	11.26	5.11	1.75	87.73
≥75	0.00	0.25	3.66	5.68	2.20	0.54	100.06
Cumulative percent by hematocrit level	0.10	3.46	33.25	74.34	92.87	100.00	

[a]Based on data from approximately 13,200 patients tested by National Medical Care. Data do not distinguish among patients' method of dialysis.
b Total does not sum to 100 because of rounding.
SOURCE: Berger, 1989 (11).

It is estimated that one-fourth of dialysis patients undergoing hemodialysis require regular or intermittent blood transfusions to maintain acceptable hematocrit levels (57). At initial administration, blood transfusions produce a quick increase in hematocrit, but as the red blood cells die, the hematocrit level drops and another transfusion is required. Thus, it is difficult to stabilize a patient's hematocrit level with blood transfusions. In addition, many risks are associated with repeated blood transfusions, such as iron overload and the potential for transmission of various types of hepatitis virus or the human immunodeficiency virus (HIV) (65). A more detailed discussion of the risks associated with blood transfusions is found later in this chapter. Whether a patient receives a blood transfusion depends on several factors, such as the patient's hematocrit level, signs and symptoms of anemia, and the clinician's judgment. Androgens are male hormones capable of stimulating erythropoiesis, but are associated with side effects, such as liver toxicity and masculinization, and are used infrequently (104).

EVALUATION OF THE EFFICACY OF RECOMBINANT erythropoietin

A safe and efficacious treatment for anemia associated with chronic renal failure has been unavailable. Efficacy refers to the probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use (143).

The efficacy of recombinant erythropoietin has been assessed primarily by physiologic factors, including changes in hematocrit level and reduction in the need for blood transfusions, an indication that anemia has been alleviated. Although information from studies does not indicate that use of recombinant erythropoietin increases length of life, evidence suggests that the biologic increases the hematocrit level, reduces the need for blood transfusions, and improves aspects of the quality of life of dialysis patients, such as well-being and activity level. The efficacy of recombinant erythropoietin for conditions besides chronic renal failure is being explored.

Physiologic Effects of Recombinant erythropoietin in Chronic Renal Failure Patients

Studies in the United States to determine the efficacy of recombinant erythropoietin were first performed in chronic renal failure patients, including dialysis and predialysis patients. Three different classes of studies were done: randomized studies in which there was an untreated or placebo-treated control group; randomized studies in which there was no untreated control group and a before and after effect was examined; and studies in which there was no randomization, and a before and after effect was examined.[4] Important characteristics of some of these studies are listed in table 2-4.

The studies indicate that recombinant erythropoietin produces a dose-dependent increase in hematocrit levels and can reduce or eliminate the need for blood transfusions in most patients.[5] The time required to increase the hematocrit level (rate of increase) and the amount of increase depend on the dose.

In June 1989, the Food and Drug Administration (FDA) approved recombinant erythropoietin for administration by the intravenous route in dialysis patients[6] and by both the intravenous and subcutaneous routes in predialysis patients (160).

A In a randomized trial, patients are randomly assigned to a control group, which receives standard or no therapy, or to an experimental group, which receives the intervention being assessed. In a before and after trial, the patients' physiological parameters serve as the baseline to assess the impact of the intervention.

5 According to the Food and Drug Administration (FDA), transfusion-dependency was defined as requiring at least six transfusions per year (159).

6 The intravenous route of administration of recombinant erythropoietin was used in hemodialysis patients because of the availability of an access site to the blood stream to which the dialysis machine is connected. The subcutaneous route of administration of recombinant erythropoietin, which is used for both predialysis patients and peritoneal dialysis patients, is more practical for these patients because of the unavailability of an intravenous access site.

Table 2-4-Efficacy and Safety Studies in Chronic Renal Failure Patients

Study design	Number of patients	Target hematocrit	Doses used and results	Significance level (p value)	Source[a]
A	89 HD	see results	IV dose of 100 units/kg produced increase in hematocrit from 22 to 34 vs. placebo (22 to 23).		Sobota, 1989 (131).
A	101 HD	32-38	IV dose of 150 units/kg or placebo TIW for 12 weeks. 97 percent reached target hematocrit.	0.0005	U.S. DHHS FDA 1989 (160).
B	131 HD	see results	IV doses of 25 units/kg, 100 units/k& and 200 units/kg increased the hematocrit from 22 to 28,21 to 32, and 21 to 32 respectively over 138 days.	NA	Sobota, 1989 (131).
C	333 HD	32-38	IV doses of 300 units/kg; or 300 units/kg reduced to 150 units/k& or 150 units/kg for 12 weeks. Mean maintenance dose was 108 units/kg. 97 percent reached target hematocrit.	0.0005[b]	Eschbach, et al., 1989 (56).
A	14 PD	3541	IV doses of 50, 100, and 150 units/kg compared with placebo in 14 patients. Over 8 weeks, increases in hematocrit were 27 to 35,27 to 36,28 to 41, and 24 to 28, respectively.	O.0001	Lim, et al., 1989 (92).
A	12 PD	36	SC dose of 100 units/kg or placebo. Hematocrit increased in 11 patients from 25 to 36 after 3 months. 92 percent reached target hematocrit.	0.001	Teehan, et al., 1989 (140).
A	93 PD	38-40	SC dose of 100 units/kg (45) or placebo (48). 58 percent reached target hematocrit.	NA	U.S. DHHS FDA 1989 (160).
A	117 PD	3540	IV doses of 50,100, and 150 units/kg were compared with placebo in initial phase. Hematocrit increased 0.13,0.20,0.26, and -0.01 points/day respectively. Patients then treated SC or IV (75-150 units/kg) in maintenance phase. 94 percent reached target hematocrit.	NA	U.S. DHHS FDA, 1989 (160).
B	17 PD	3740	SC doses of 50-100 units/kg and IV dose of 150 units/kg in initial phase; SC maintenance doses at levels to sustain hematocrit.	O.0001	Eschbach, et al.,1989 (58).
c	5 CAPD (Pediatric)	32-38	SC dose of 150 units/kg TIW increased hematocrit from 22 to 33.	0.001	Sinai-Trieman, et al., 1989 (130).

[a]Numbers in parentheses refer to list of references.
[b]Compared to patients' initial hematocrit levels.

KEY: A = randomized clinical trial that employed placebo or untreated control; B = randomized clinical trial that did not employ placebo or untreated control and a before and after effect was examined; C = nonrandomized trial in which a before and after effect were composed; CAPD = continuous ambulatory peritoneal dialysis; HD = hemodialysis; IV = intravenous; kg = kilogram; NA = not available; PD = predialysis; SC = subcutaneous; TIW = 3 times weekly.

FDA's approved labeling for recombinant erythropoietin recommends that there be initial dosing and maintenance dosing phases. According to the labeling, therapy should start with 50-100 units/kg of recombinant erythropoietin 3 times a week by intravenous administration for 6 to 12 weeks. When the hematocrit reaches the target range of 30-33 percent, or rises by more than 4 points in any 2-week period, the labeling recommends that the dose be reduced by 25 units/kg. An individual should be maintained in the target range by adjusting the dosage by 25 units/kg of body weight at 2-6 week intervals (160).[7] The maintenance dose is usually lower than the induction dose once the target hematocrit is attained.

At doses of 50 units/kg, the hematocrit increased 0.11 points/day, and at 100 units/kg, it increased 0.18 points/day, clearly establishing a dose-response relationship (160). To maintain patients in the 34-36 percent hematocrit level, 65 percent of patients required fewer than 100 units/kg 3 times weekly; 10 percent each required either fewer than 50 units/kg or more than 200 units/kg 3 times weekly (160).

FDA reviewed data to show the comparability of intravenous and subcutaneous administration for chronic renal failure (62). However, neither the FDA Summary Basis of Approval nor the FDA-approved labeling addresses the relative efficacy of the intravenous route vs. the subcutaneous route of administration, or the relationship between efficacy and dose by these respective routes.

Studies clearly indicate that intravenous recombinant erythropoietin produces a significant rise in hematocrit level in those patients who are treated as compared with those not treated. Although the populations used in the studies may be representative of the age distribution of the dialysis population as a whole, little differentiation was made in the interpretation of the results of the studies, however, of the effect by age group. Evaluating this dimension becomes particularly important as the number of elderly dialysis patients increases (46).[8]

In a large clinical study, 101 anemic hemodialysis patients were randomized to receive either placebo or intravenous recombinant erythropoietin, 150 units/kg of body weight 3 times weekly for 12 weeks (160). In the second 12-week phase, the control group was given the same dose of recombinant erythropoietin as the experimental group. The target hematocrit of 35 percent was attained by a cumulative 95 percent of the patients, with the target hematocrit's being achieved by 97 percent of patients in the original treatment group and 93 percent of patients in the control group after crossover to experimental treatment. Information on statistical significance levels was not presented.

In another study without an untreated or placebo-treated control group, 333 patients (ages 18-81) were randomized to receive doses of either 300 or 150 units/kg, which was then reduced to 75 units/kg when the target hematocrit of 32-38 percent was reached (56). In 97.4 percent of patients, hematocrit increased from 22.5 percent to 35 percent ($p<.0005$) within the first 12 weeks. The average hematocrit level was maintained at 33.8 percent after 6 months of treatment ($p<.0005$) and 35.5 percent after 10 months of treatment ($p< .0005$). The group receiving the higher dose reached the target hematocrit more quickly than did the group receiving the lower dose (6-8 weeks for the higher dose group vs. 10 weeks for the lower-dose group).

7 As an alternative to using a higher dose during the initial phase and a lower dose in the maintenance phase, a model was recently developed that may allow clinicians to determine an optimal dose from the initiation of therapy. The model is based on survival time of red blood cells in the body and dose-response cures that were developed in earlier studies (67).

8 Elderly patients are more susceptible to the adverse and toxic effects of most drugs. Changes with aging in body composition and in drug distribution, metabolism, excretion, and response make elderly people more vulnerable to adverse reactions. Since most clinical trials and pharmacological studies are performed in younger people, it is often hazardous to apply drug treatment standards developed for these populations to the elderly (12).

In the same study, after 8 weeks of therapy, none of the treated patients was dependent on blood transfusions, including 116 previously transfusion-dependent patients. An average 0.52 units of blood per patient per month had been required before initiation of recombinant erythropoietin therapy. These requirements were reduced to 0.1 units per patient per month after the first 4 weeks of therapy, and 0.04 units or fewer per patient per month during the study.[9] (The impact of recombinant erythropoietin on reducing blood transfusion requirements in chronic renal failure patients is described in table 2-5).

9 This study did not specify the volume in a unit of blood. For dialysis patients, a transfusion usually consists of 250 ml. of packed red blood cells (77).

In a before and after study, recombinant erythropoietin was intravenously administered over a range of doses between 15 and 500 units/kg to 25 anemic hemodialysis patients (ages 21-69, hematocrits 15 percent to 24.5 percent) (57). Dose-dependent increases in erythropoiesis were noted over 3 to 7 months. Blood transfusions were no longer needed by 12 patients, the only patients that received them before recombinant erythropoietin was used.

A before and after study of 5 transfusion-dependent pediatric peritoneal dialysis patients ages 12-18 was undertaken. In the 6 months preceding recombinant erythropoietin therapy, each patient had received between 5 and 18 blood transfusions to

Table 2-5-Reduction in Blood Transfusions with Recombinant erythropoietin Therapy

Study design	Number of patients	Results	Source[a]
A	244 HD[b]	In first randomized arm, the transfusion requirements of 113 treated patients receiving 100 units/kg of recombinant erythropoietin were reduced from 0.17 units per patient per week to 0.09 per week over 6 weeks versus the placebo group, which remained at 0.19 units, per patient per week. In the second randomized arm, transfusion requirements of 131 patients were reduced from 0.09 units per patient per week to 0.04 units per patient per week over 6 weeks vs. the placebo group, which increased from 0.18 units per patient per week to 0.22 units per patient per week after 6 weeks.	Sobota, 1990 (132a).
B	131 HD	After 4 weeks, 4 patients treated with 25 units/kg had a reduction in total transfusions from 69 to 25; 44 patients treated with 100 units/kg had a reduction in total transfusions from 70 to 12; 43 patients treated with 200 units/kg had a reduction in total transfusions from 93 to 18.	Sobota, 1990 (132a).
C	333 HD	Patients needed an average 0.52 units of blood per month prior to therapy; this decreased to 0.1 units per patient per month after 4 weeks, and virtually all patients were transfusion-independent after 12 weeks.	Eschbach, et al., 1989 (58).
C	25 HD	18 patients required transfusions in the 6 months prior to therapy, and 12 were transfusion-dependent, requiring transfusions at least twice a month. These requirements were eliminated in all patients after therapy.	Eschbach, et al., 1987 (57).
C	5 CAPD	In the 6 months before therapy, patients needed 5 to 18 blood (Pediatric) transfusions each; these requirements were eliminated after 12 weeks.	Sinai-Trieman et al., 1989 (130).

[a]Numbers in parentheses refer to list of references. Another report estimated that tranfusion-dependent patients required 7.1 units per year and that these could be eliminated with recombinant erythropoietin therapy (117).

[b]Study consisted of two separate randomized arms.

KEY: A = randomized clinical trial that employed placebo or untreated control; B = randomized clinical trial that did not employ placebo or untreated control and a before and after effect was examined; C = nonrandomized trial in which a before and after effect was examined; CAPD = continuous ambulatory peritoneal dialyis; HD = hemodialysis; kg = kilogram.

maintain a hematocrit of 20 percent and treat symptoms of anemia. The children were treated at home with 150 units/kg recombinant erythropoietin subcutaneously 3 times weekly for 5 to 8 months. The hematocrit level increased from an average of 22 percent to an average of 33 percent ($p < 0.001$), and was maintained in the 32-38 percent range for 5 to 8 months. When the patients reached the target of 35 percent, the dose was decreased in increments of 25 units; when the level reached 40 percent, treatment was discontinued until the hematocrit dropped below 40 percent. The patients were then reinstated on a dose of 150 units/kg once or twice weekly subcutaneously to maintain their hematocrit levels. Further blood transfusions were not required when the target hematocrit was reached (130).

Reflecting the dose-response relationship to recombinant erythropoietin, the time to reach a target hematocrit level and the number of patients reaching any specified target depend on the dose used (see table 2-6). Although the study designs are not presented, it appears from the data that doses of 100 units/kg are needed for 90 percent or more of patients to respond. The data also suggest that with doses of 44 units/kg, slightly more than 50 percent of patients respond. Lower doses seem to produce a lower response rate in a smaller number of patients. In one case, approximately 70 percent of patients (n= 116) in a before and after study without randomization increased their hematocrits to 30 percent over 12 weeks with only 50 units/kg 3 times weekly (18).

Studies to date, as indicated in table 2-7, suggest that subcutaneously administered recombinant erythropoietin is also efficacious at both increasing and maintaining the hematocrit level of most patients to whom it is administered. The current evidence is more voluminous for the efficacy of the subcutaneous route of administration in predialysis patients than in dialysis patients. One report does indicates efficacy in dialysis patients (17).

The evidence is clearly convincing that both the subcutaneous and intravenous routes are efficacious in increasing hematocrit levels. Although some have suggested that target hematocrit levels can be attained with lower doses by the subcutaneous route, there are not enough data to fully support this conclusion. No study compared the same doses by different routes of administration. In most of the studies, both the routes of administration and the doses were varied, making comparison difficult.

In some cases, lower doses of subcutaneously-administered doses of recombinant erythropoietin were able to achieve a similar therapeutic response as higher doses of the intravenously-administered product. This usually occurred, however, over a longer period of time. For example, in one study, the target hematocrit was reached in 8 weeks with 150 units/kg intravenous recombinant erythropoietin as compared with 12 weeks with 100 units/kg of subcutaneous recombinant erythropoietin (58). one possible explanation is that subcutaneously admin-

Table 2-6-Dose Response to Intravenous Recombinant erythropoietin

Dose used (units/kg)	Number of patients	Percent responding	Source
300/150	309	97	Eschbach, et al., 1989 (58).
200	43	>90	Sobota, 1989 (131).
120	2%	93	Kuhn, et al., 1988 (186).
100	44	>90	Sobota, 1989 (131).
80	2a	82	Kuhn, et al., 1988 (186).
50	116	71	Blagg, 1989 (17).
44	236	55	Roxas, 1989 (122).
40	29	28	Kuhn, et al., 1988 (186).
25	44	<25	Sobota, 1989 (131).

a Response was considered an increase in hematocrit to over 30 percent in 3 months.
Numbers in parentheses refer to list of references.

KEY: kg = kilogram.

SOURCE: Eschbach, and Adamson, forthcoming, 1990 (55).

Table 2-7-Studies of Subcutaneous Administration of Recombinant erythropoietin

Study design	Number of patients	Dose[a]	Results	Significance level (p value)	Source[b]
A	14 PD	SC doses of 100 units/kg or placebo	Average hematocrit increased for treated group from 2 35.8 percent over 12 weeks. Average hematocrit remained at 28 percent for placebo group.	0.004	Kleinman, et al., 1990 (83).
A	12 PD	SC doses of 100 units/kg or placebo	Hematocrit increased in 11 patients from 25 percent to 36 percent after 3 months.	0.001	Teehan, et al., 1989 (140).
A	93 PD	SC doses of 100 units/kg (45) or placebo (48)	Hematocrit of 38-40 percent attained by 58 percent of treated vs. 4 percent placebo in 12 weeks.	NA	US DHHS, FDA, 1989 (160).
A	117 PD	SC or IV doses of 75-150 units/kg in maintenance phase after target hematocrit of 35-40 percent reached.	Hematocrit maintained in 36-38 percent range for 6 months in 94 percent of patients.	NA	US DHHS, FDA, 1989 (160).
B	17 PD	IV doses of 50-100 units/kg and SC doses of 150 units/ kg in initial phase. Maintenance dose given SC at levels to sustain increase in hematocrit.	Hematocrit increased from 28 percent to 37 percent in 12 weeks by SC and 8 weeks by IV.	0.0001	Eschbach, et al., 1989 (58).
C	5 CAPD (Pediatric)	SC doses of 150 units/kg	Hematocrit increased from 22 percent to 33 percent.	0.001	Sinai-Trieman, et al. 1989 (130).
C	12 CAPD	Initial SC doses of 100 and 150 units/k& reduced to 50 units/kg.	Hemoglobin increased 2 g/dl over 26+ weeks, reaching 11 to 11 1/2 g/all in 11 patients.[c]	NA	Stevens, et al., 1989 (134).
C	86 HD[a]	IV doses averaged 101 units/kg in 55 patients and SC doses averaged 108 units/kg in 31 patients.	Patients treated IV maintained target HCT for 23 months; patients treated SC maintained HCT for 21 months.		Blagg, 1990 (17).
C	29[e]	Doses, routes, and frequency of administration were varied.	Hemoglobin was maintained in target (10.5 < Hb < 13) at doses of 80 units/kg SC weekly in 13 patients and 164 units/kg SC twice weekly in 16 patients.	NA	Besarab, et al., 1990 (13).

administered three times weekly, unless otherwise noted.

b Numbers in parentheses refer to list of references.

[c] Hemoglobin is the oxygen-carrying protein of red blood cells. Normal average hemoglobin levels in men are 14-18 g/all (grams/deciliter) and 12-16 g/all for women (12).

d study compared administration in home dialysis with ***in-center dialysis patients.***

'Abstract did not report the patients' methods of dialysis.

KEY: A = randomized clinical trial that employed placebo or untreated control; C = nonrandomized trial in which a before and after effect was examined; CAPD = continuous ambulatory peritoneal dialysis; HCT = hematocrit; HD = hemodialysis; IV = intravenous; kg = kilogram; NA = not available; PD = predialysis; SC = subcutaneous; TIW = three times **weekly.**

istered product is stored in the muscle tissues and released into the blood stream over a period of time, in contrast to intravenous product, which is released into the blood stream immediately upon injection. The benefit of very high peak serum levels after an intravenous injection seems to be questionable (105). The differences in the doses used maybe the primary reason for this phenomenon, however. In the final analysis, additional randomized trials with control groups in larger patient groups are needed to compare the relative efficacy of these two routes.

Patients that perform dialysis at home are most likely to self-administer recombinant erythropoietin by the subcutaneous route. If the patient self-administers the product correctly, there is every reason to believe that the product will be efficacious. Training to perform self-administration will most likely come from the patient's physician and will include instructions on how to store the product (e.g., refrigeration), how to draw up the product from the vial using sterile technique, and how to inject the needle. In addition, it will be important for patients that self-administer the product to have their hematocrit and iron stores checked regularly (17).

Evidence of the efficacy of self-administration of recombinant erythropoietin by patients is limited to a few reports. In one before and after report, 5 hemodialysis patients (ages 18-55) who self-administered recombinant erythropoietin intravenously through the arteriovenous graft over a 3-month period had a mean rise in hematocrit from 18.4 percent to 32.6 percent (110). None of the patients required further blood transfusions. In another before and after report, 17 patients maintained their target hematocrit by administering recombinant erythropoietin subcutaneously at home (82). The dose used to maintain the target hematocrit was tailored to the individual patient's needs. Finally, in a study comparing 55 in-unit dialysis patients treated intravenously with an average of 101 units/kg with 31 home dialysis patients, the home patients were able to maintain for 21 months the hematocrit level attained in the dialysis center in a self-administration program with intravenous doses of 108 units/kg of recombinant erythropoietin (18).

Effect of Recombinant Erythropoietin on Quality-of-Life in Chronic Renal Failure Patients

The efficacy of recombinant erythropoietin therapy may be measured by its impact on an individual's quality of life, a multifaceted, multidimensional concept. The quality of life may be assessed by measures that relate to such aspects as ability to work, level of functional impairment, well-being, psychological attitude, and life satisfaction (59).

The quality of life of chronic renal failure patients may be affected by several factors, such as the severity and number of the patient's underlying illness or illnesses, the treatment approach (dialysis vs. transplantation), the symptoms associated with anemia of chronic renal failure, and the characteristics of the dialysis and transplant centers, since patients at certain centers seem to be better rehabilitated than those at other centers (59).

The symptoms of anemia may impair the well-being and functioning of dialysis patients. Hypoxia due to anemia associated with chronic renal failure often leads to persistent lethargy, decreased exercise tolerance, poor appetite, and decreased sexual performance. From a theoretical point of view, any increase in the hematocrit should result in increased central and peripheral oxygen availability and enhance exercise capabilities and the quality of life. Because of the many medical and social problems confronting dialysis patients, however, alleviating the symptoms of anemia may only partially contribute to an improved quality of life. Treatment for this anemia, generally consisting of blood transfusions, can produce adverse reactions that effect patients' quality of life. In addition, therapies used to treat other underlying medical conditions, such as drugs, may have debilitating side effects. For example, drug therapy for treating diabetes and hypertension may produce side effects such as lethargy or sexual impotence, which are also common symptoms of anemia.

The time involved in undergoing regular dialysis treatments at home or traveling to a center to receive such treatments may prevent dialysis patients from

developing and maintaining a regular work schedule. This can affect a patient's perception of self-worth and result in financial hardships that affect lifestyle. Thus, when the efficacy of recombinant erythropoietin is considered, it is important to recognize that multiple factors contribute to the quality of life of dialysis patients.

With one exception, the information on recombinant erythropoietin's impact on quality of life comes primarily from randomized or before and after studies of hemodialysis patients in which there was no control group. These quality-of-life studies suggest that correction of anemia associated with chronic renal failure with recombinant erythropoietin can improve the functional abilities of chronic renal failure patients (see table 2-8).

One randomized study examining the quality-of-life involved 118 hemodialysis patients. After 6 months of treatment with recombinant erythropoietin, clinically and statistically significant improvements in the sickness impact profile ($p< 0.02$), stress test ($p< 0.0018$), and other quality-of-life indicators were noted (physical symptoms, fatigue, relationship with others) as compared with the control group (26).

A randomized study evaluated quality-of-life changes in 17 predialysis patients (58). Investigators described subjective improvement in well-being and appetite in the patients. Predialysis patients continued to work and be active, even though their renal functions continued to deteriorate. The quality of life of patients who were not on therapy was not reported, however, making comparison to the treated group impossible.

A recent before and after study examining the relationship between recombinant erythropoietin therapy and quality of life in 333 hemodialysis patients supports earlier findings. Statistically significant increases in hematocrit were noted in patients treated with recombinant erythropoietin over a 4.4 month period and sustained over an average of 10.3 months ($p < 0.001$). Improvements in the quality of life were measured by the Karnofsky index ($p < 0.01$) and subjective quality-of-life indicators, such as well-being ($p < 0.004$), psychological affect ($p < 0.03$), and life satisfaction (p c 0.017). The use of the Nottingham Health Profile produced mixed results, with statistically significant improvements in some measures (energy, emotional reaction) and not in others (pain, sleep, mobility). The number of patients who returned to work after the 10.3 months of treatment was not significantly different from those working at baseline (61).

After the first period, patients reported statistically significant improvements in activity and energy levels ($p<0.01$), which were correlated with statistically significant increases in hematocrit over baseline ($p< 0.01$). Patients reporting low energy levels at the beginning of the study dropped by half after the first period of the study. Improvements reported after the first period of the study were maintained through the entire study period of about 10 months.

A Nottingham profile index was used to measure patient energy levels. A measure of O indicated "no limits" on energy levels, while a measure of 100 indicated complete limits. The patients' average energy level limitation score at the beginning of the study was 47, fell to 31.5 after the first phase of the study, and measured 17.7 at the end of the study ($p< 0.01$). Information on the mean age and other underlying disease states in the patients was not reported. The increase in energy levels was not reported by age group.

A Karnofsky score index was used in another before and after to measure the rehabilitation of 29 dialysis patients (64). (A score of 91-100 indicates ability to engage in full activities without significant effort, while 81-90 indicates ability to engage in usual activities with some effort.) The mean score for the patients increased from 76 to 86.6. Although the significance level was not included, a statistically significant increase in the score was reported for all patients in age groups 20 to 69, but not for those patients aged 70 or over.

In summary, reports to date suggest that recombinant erythropoietin has the potential to improve dialysis patients' quality of life. Long-term studies in the chronic renal failure population are needed, and the relationship between recombinant erythropoietin

Table 2-8-Quality-of-Life Studies

Study design	Number of patients	Physiologic results	Quality-of-Life results	Significance level (p value)	Source[a]
A	118 HD	After 5 months hemoglobin averaged 7.4 g/all for the placebo group, 10.2 g/all for one treatment group (target 95-10.0 g/all), and 11.7 g/all for the other treatment group (target 11.5-13.0 g/all).	Sickness Impact Profile improved, stress test improved	0.02 0.018	Canadian EPO Study Group, 1989 (26).
c	333 HD	Hematocrit rose from less than 30 to 35 after 4.4 months and stayed at 34 after 10.3 months.	Karnoksfy score increased from 27 percent to 48 percent. Ability to work: -patient reported -staff reported Subjective quality of life -well-being -psychological affect -life satisfaction	0.01[b] 0.69 0.93 **0.004** **0.03** **0.017**	Evans, et al., 1990 (61).
C	68 HD	Hematocrit rose from 22.9 to 33.5.	Increase in energy, body temperature, appetite sleep, hair growth, sexual interest.	NA	Eschbach and Adamson, 1989 (54).
C	130 HD	Hematocrit rose from 23.7 to 34.2 (after 5.6 months) to 33.9 (after 9.7 months)	Increase in categories of no complaints, activity energy, and energy limit, as measured by Nottingham profile.	0.01	Evans, et al., 1989 (60)[c].
C	45 HD	Hematocrit rose from 19.3 to 39.8	Appetite, cold tolerance, sleep, sex function, skin color, hair growth increased.	NA	Delano, et al., 1989 (42)[c].
C	37 HD	Hematocrit rose from 19.3 to 31.5. 32 patients remained in study for 2 years.	Well-being appetite, sexual function increased. Karnofsky score used to measure increased range of activities.	NA	Gibilaro, et al., 1989 (64)[c],
C	8 HD	Hematocrit rose from 17.3 to 33.3.	Improvement in exercise capacity	**0.002**	Meyer, et al., 1988 (100).
C	17 HD	Hematocrit rose from 22.7 to 36.6.	Central nervous system functional status increased.	NA	Nissenson, et al., 1989 (106)[c].
C	17 HD	Statistically significant increase in hematocrit noted.	Conceptual and visual motor skills increased.	NA	Wolcott, et al., 1989 (173)[c].
C	17 PD	Statistically significant increase in hematocrit.	Well-being and appetite increased.	NA	Eschbach, et al., 1989 (58).

a Numbers in parentheses refer to list of references.
b P values from baseline to 10.3 months.
c This study reported on a subset of the 333 patients in Evans, et al., 1990 (61).
Nissenson, et al., 1989 (106) and Wolcott, et al., 1989 (173) report on the same 17 patients.

KEY: A = randomized clinical trial that employed placebo or untreated control; B = randomized clinical trial that did not employ placebo or untreated control, but a before and after effect was examined; C = nonrandomized trial in which a before and after effect was examined; HD = hemodialysis; NA = not available; PD = predialysis.

therapy and the ability to work in the case of predialysis patients or ability to return to work in the case of dialysis patients needs to be explored. Determining the long-term effect of recombinant erythropoietin on the quality of life is important because a number of factors contribute to this dimension. Recombinant erythropoietin may produce initial short-term improvements in patients that may or may not persist in the long-term. Finally, future studies should report impact on quality of life by age group, particularly the elderly, since they will constitute a larger percentage of the dialysis population in the near future, and previous studies have presented little information on this age group.

The potential to undertake quality-of-life studies increases as the number of patients on long-term recombinant erythropoietin therapy increases. The ability to find patients that are not being treated with recombinant erythropoietin for the purpose of serving as a control group for such studies, however, may become difficult or impossible. Patients may have to serve as their own control group, or the results from past quality-of-life studies of dialysis patients may serve as potential controls.

Other Potential Uses of Recombinant erythropoietin

The literature suggests that recombinant erythropoietin may be effective in correcting anemias associated with other medical conditions. Because insufficient endogenous erythropoietin production may only partially contribute to these anemias, careful evaluation of the efficacy of recombinant erythropoietin must be made for each condition.

Studies of the safety and efficacy of recombinant erythropoietin in other medical conditions are in various stages. Furthest along in the process are studies in anemia: associated with HIV, which is responsible for acquired immunodeficiency syndrome (AIDS). Ortho Pharmaceutical Corporation submitted a Product Licensing Application (PLA) to FDA for this indication in February 1989 (l).

Anemias Associated With the Human Immunodeficiency Virus (HIV)

Anemia associated with HIV appears to be prevalent among infected people. Recent data indicate that up to 71 percent of patients with AIDS are anemic (hemoglobin value of less than 14 g/dl).[10] In addition, patients with other HIV-related symptoms also have some level of anemia. For example, about 63 percent of AIDS patients with Kaposi's sarcoma,[11] 20 percent of patients with AIDS-related complex (ARC),[12] and 8 percent of patients who are infected with the HIV virus and asymptomatic, are also anemic (175).

In contrast to anemia associated with chronic renal failure, multiple factors are responsible for anemia in people infected with HIV. These include insufficient bone marrow stores as an adverse effects of drug treatment. For example, anemia is a common complication of therapy with zidovudine (37), the only drug currently approved as effective against HIV.[13] FDA has approved zidovudine for treating AIDS and ARC and, more recently for retarding progression of the disease in certain infected people who have not yet developed symptoms (163).

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10 Hemoglobin is the oxygen-carrying protein of red blood cells and can also be used as a measure of anemia. Normal hemoglobin values in men are 14-18 g/all (grams/deciliter) and 12-16 g/all for women (12).

11 Kaposi's sarcoma is a multifocal, spreading cancer of connective tissue, principally involving the skin; it usually begins on the toes or the feet as reddish blue or brownish soft nodules and tumors. Previously seen in older men of Jewish or Mediterranean descent, Kaposi's sarcoma is now one of the opportunistic diseases occurring in AIDS patients.

12 AIDS-related complex is a variety of chronic but nonspecific symptoms and physical findings that appear related to AIDS and that may consist of chronic generalized lymphadenopathy, recurrent fevers, weight loss, minor alterations in the immune system, and minor infections.

13 Zidovudine is the generic name for Retrovir, also known as AZT.

A randomized study of AIDS patients treated with AZT (1,500 mg/day) or placebo for up to 24 weeks indicates the extent to which AZT can cause anemia. More than half of the 83 AZT-treated patients (46) required transfusions during the treatment period vs. only 15 of the 74 placebo-treated patients (119).

One randomized study with a control group has evaluated the efficacy of subcutaneously administered recombinant erythropoietin in 63 AIDS patients taking zidovudine. The trial produced mixed results; as one would expect, those patients with low levels of endogenous erythropoietin responded better than those patients with high levels. At the beginning of the study, 23 of 29 patients receiving recombinant erythropoietin required blood transfusions. At the end of the study, 11 of these patients still needed transfusions. In the control group of 34 patients, 27 required transfusions before the study and 21 still required them after the study. Some patients in the treated group reported improvement in energy level, work capacity, and quality of life (108).

The results of another randomized trial support the notion that recombinant erythropoietin corrects anemia associated with zidovudine treatment in only a subset of the population, primarily those individuals with low endogenous stores of erythropoietin. There were statistically significant changes in the hematocrit level ($p=0.0002$) from baseline for patients with low circulating erythropoietin levels (less than 500 milliunits/milliliter) vs. placebo-treated patients. Alternatively, patients with high levels (greater than 500 milliunits/milliliter) did not have a statistically significant increase in hematocrit, nor was the increase in hematocrit statistically different from the placebo-treated patients in the same group (174).

In contrast to chronic renal failure patients treated with recombinant erythropoietin, there was little relationship between hypertension, seizures, and the use of recombinant erythropoietin in HIV-infected patients (174).

Anemia Associated With Rheumatoid Arthritis

Another potential use of recombinant erythropoietin is to treat anemia associated with rheumatoid arthritis, a progressive, chronic, inflammatory disease that can lead to irreversible joint damage. Anemia associated with arthritis usually results from the bone marrow's inability to respond to endogenous erythropoietin ***(23).*** Therefore, exogenous erythropoietin may have limited therapeutic use in this condition. In one observational study, 2 patients with rheumatoid arthritis treated over a 5-month period (with 100-200 units/kg intravenously three times a week) experienced an increase in hematocrit level from 32 and 30 percent to 43 and 39 percent, respectively, during the treatment period (98).

Autologous Blood Transfusions

Recombinant erythropoietin may be used for patients who want to donate their own blood for potential transfusions during elective surgery, commonly referred to as autologous blood transfusion. The transfusion of homologous blood, or blood from another person, may be associated with various adverse effects, including rejection of the blood if improperly matched and risk of transmission of certain viral infections. The use of autologous blood also reduces the demand on the nation's blood supply.

Current autologous blood donation averages only 2.2 units of blood over a 2-to 5-week period (141). In addition, there is usually a significant time lag between donations, which could delay surgical procedures. The American Association of Blood Banks recommends a minimum hematocrit value of 34 percent and a 7-day period between donations of blood from autologous donors (72). In a randomized controlled study of 47 adults scheduled for elective orthopedic surgery, either recombinant erythropoietin (600 units/kg 2 times a week intravenously) or placebo was administered for 21 days. The mean number of units of blood collected was 5.4 for the group treated with erythropoietin and 4.1 for the placebo group ($p<0.05$) (66).

Other Anemias

The use of recombinant erythropoietin in correcting cancer-related anemias is currently under investigation. Cancer-related anemia usually results from increased destruction of red blood cells and decreased erythropoiesis due to kidney damage from cancer treatments, such as radiation and chemotherapy. A recent abstract suggested that anemia of cancer may be due to the malignancy itself or may be caused by antineoplastic agents (101). The data suggested that both treated and untreated cancer patients may have low levels of endogenous erythropoietin.

Recombinant erythropoietin has also been used in treating anemia of Gaucher's Disease, an inherited disorder of lipid metabolism (121), and in treating anemia of preterm infancy (87). No studies on efficacy have been done in these conditions to date.

EVALUATION OF THE SAFETY OF RECOMBINANT erythropoietin

Adverse Effects of Recombinant erythropoietin

In evaluating the safety of recombinant erythropoietin, it is important to distinguish among those adverse effects that are attributable to the product itself versus those that result from the natural progression of chronic renal failure. For example, both hypertension and seizures, adverse effects attributable to recombinant erythropoietin,

Table 2-9-Adverse Reactions to Recombinant erythropoietin

Study design	Number of patients	Adverse reactions reported	Source[a]
A	375 HD[b]	The most frequently reported adverse reactions for all patients were nausea, fever, chest pain, fatigue, pain, dizziness, dyspnea, vomiting, upper respiratory infection. 92 percent of treated patients in randomized phases had one or more adverse reactions vs. 83 percent untreated patients.[c] The incidence of headache and clotting of placebo of the access site appeared to be related to treatment.	Sobota, 1989 (131).
A	14 PD	An increase in antihypertensive medication was needed in 3 treated patients.	Lim, et al., 1989 (92).
B	17 PD	14 of 17 patients were taking antihypertensives. 9 had an increase in blood pressure with additional antihypertensives needed. 2 originally normotensive patients needed antihypertensives.	Eschbach, et al., 1989 (58).
C	333 HD[d]	44 percent of normotensive patients (n = 71) developed hypertension and 32 percent of the 71 patients needed antihypertensives. 72 percent of hypertensive patients (n= 180) had an increase in blood pressure, and 32 percent of the 180 patients needed additional antihypertensives. 43 percent developed iron deficiency (would have been 20 percent greater if some patients were not iron overloaded from blood transfusions). 5.4 percent had seizures (in 18 of 333 patients; 10 of 18 occurred in first 3 months of therapy).	Eschbach, et al., 1989 (56).

a Numbers in parentheses refer to list of references.
b The trial consisted of an initial randomized dose-response phase (n=131) without placebo control. Two later phases were randomized, placebo-controlled (n=244). The total number of patients in study was 375.
[c] An adversereactionwas defined as any event that occurred to patients,whether relatedor unrelated to the intervention.
Of 333 patients in the study, data for 251 patients were sufficient to evaluate changes in blood pressure.

KEY: A = randomized clinical trial that employed placebo or untreated control; B = randomized clinical trial that did not employ placebo or untreated control and a before and after effect were examined; C = nonrandomized trial in which a before and after effect were examined; HD = hemodialysis; PD = predialysis.

Table 2-10-Percent of Patients Reporting Adverse Reactions from Recombinant erythropoietina

Adverse reaction	Treated patients (n=200)	Placebo patients (n= 135)
Hypertension	24.0	18.5
Headache	16.0	11.9
Muscle aches	11.0	5.9
Nausea	10.5	8.9
Swelling	9.0	10.4
Access to graft clotted	6.8	2.3
Seizure	1.1	1.1
Cerebrovascular accident	0.4	0.6

a Based on events reported in placebo-controlled studies in patients with chronic renal failure. Levels of statistical significance are unavailable.

SOURCE: Amgen, Inc., 1989 (5); US DHHS, FDA, 1989 (160).

Table 2-1 l-Adverse Reactions to Recombinant erythropoietin Per Patient Year[a]

Reaction	Total treated[b]	Placebo
Hypertension		
Dialysis patients	0.69	0.33
Predialysis patients	1.70	3.28
seizure	0.0473	0.037
Clotting of arteriovenous graft	0.249-0.273	0.59

a In U.S. and non-U.S. trials.
Levels of statistical significance are unavailable.

SOURCE: US DHHS, FDA, 1989 (160).

are common complications of chronic renal failure.[14] In addition, it is important to detect any differences in adverse reactions between predialysis patients and dialysis patients, and differences in adverse reaction between patients receiving recombinant erythropoietin by the intravenous route as compared with the subcutaneous route.

Adverse reactions from recombinant erythropoietin therapy are reported in table 2-9. In chronic renal failure patients using recombinant erythropoietin, hypertension is the most prevalent adverse effect and seizures are the most serious adverse effect. Iron deficiency also occurs frequently .15 Other side effects that have been reported include headache, muscular pain, nausea, hyperkalemia,[16] and clotted access to the arteriovenous graft (160).

The potential for the development of hypertension with recombinant erythropoietin is important because of the high rate of cardiovascular morbidity and mortality in chronic renal failure patients. Although data in FDA's Summary Basis of Approval seem to indicate that there is a higher absolute incidence of hypertension in treated than untreated patients, it did not specify whether the difference is statistically significant (see table 2-10). In addition, table 2-11 indicates the incidence of adverse reactions per patient year among total U.S. and non-U.S. treated patients vs. placebo. The incidence of hypertension per patient year was twice the rate in dialysis patients as compared to placebo, but only half the rate in predialysis patients.

The literature suggests that an increase in hypertension is most likely to occur in those patients who are already hypertensive (28). Whether the development of hypertension is also related to the rate of increase in hematocrit is inconclusive (40).[17,18] Since

14Up to 90 percent of patients in renal failure are hypertensive (38). Overall, deaths from cardiovascular disease account for more than half of all mortality in renal failure patients, whether treated by dialysis or transplantation (113). Seizures occur in approximately 5-10 percent of chronic renal failure patients (160).

15Chronic renal failure patients become iron deficient because effective erythropoiesis with recombinant erythropoietin requires iron.

16Patients on recombinant erythropoietin generally experience an increase in appetite. Hyperkalemia, an increase in serum potassium, results primarily from an increase in foods that are potassium-rich. The condition, left untreated may cause cardiac problems and muscular problems (91).

17Issues of dosing of recombinant erythropoietin are important because the adverse reactions may be dose-related and the product is expensive. The target hematocrit in the FDA-approved labeling is 30-33 percent, which is lower than the hematocrit targets of most of the clinical studies, The FDA Blood Products Advisory Committee decided that the 30-33 percent range was a more appropriate hematocrit range for chronic renal failure patients because of potential side effects (62). Based on clinical studies, Amgen, Inc. initially proposed a dose of 150 units/kg 3 times weekly intravenously. FDA proposed a 50 units/kg starting dose. The committee thought the FDA-proposed initial dose was too conservative, but thought Amgen's recommended dose was too high. The committee decided on a dose of 50-100 units/kg (62).

18The increase in hypertension with recombinant erythropoietin may be attributable to two factors: the increase in blood viscosity resulting from an increase in red blood cells and an increase in peripheral vascular resistance (52).

most patients in the trials had their hypertension controlled by drugs, there is little clinical information to indicate the effect of recombinant erythropoietin on patients with uncontrolled hypertension. Nor have the studies reported the incidence of this side effect by racial or age groups.

A major unresolved issue in predialysis patients is whether exacerbation of hypertension from recombinant erythropoietin accelerates renal disease. The correction of the anemic condition in predialysis patients might result in better oxygen perfusion of organs, such as the kidney; alleviate symptoms of anemia; and increase the length of time the kidneys are able to function. Some investigators have observed that a further increase in blood pressure in hypertensive patients does not necessarily accelerate the progression of renal disease (58).

Although seizures clearly represent a significant adverse reaction to recombinant erythropoietin, it is not clear if the overall seizure rate in patients treated with recombinant erythropoietin is different from those treated with placebo or not treated at all. The rate of seizures in treated patients appears to be slightly higher in treated patients, as indicated in table 2-10; however, statistical significance data are unavailable. According to the FDA's Summary Basis of Approval, the seizure rate in treated vs. untreated or placebo-treated patients is the same; the rate is higher in the first 90 days of therapy compared with untreated or placebo-treated patients (160). There was no apparent relationship found, however, between the rate of rise of hematocrit and seizures for chronic renal failure patients experiencing a seizure during the first 90 days of treatment.

Finally, the rate of artervenous graft clotting was almost twice the rate in the placebo group as compared to the rate range in the treated group. According to the FDA's Summary Basis of Approval, the rate of graft clotting in patients treated with recombinant erythropoietin was no greater than that reported in two large independent surveys of untreated dialysis patients (160).

It is unlikely that different types of adverse reactions would occur based on the route of administration of recombinant erythropoietin. There may be some minor administration-related effects, such as pain and swelling at the site of injection after a dose of subcutaneous recombinant erythropoietin. There is some evidence to suggest that, if adverse reactions to recombinant erythropoietin are dose-related, then incidence of adverse reactions can be minimized if lower doses of recombinant erythropoietin can be given by the subcutaneous route. A slower, steadier increase in hematocrit by using low doses of the intravenous route or by using the subcutaneous route can allow clinicians to monitor response, adjust dose, and avert any cardiovascular crisis, such as seizures, if needed.

Based on clinical data available, and discussions with clinicians, it appears that self-administration of recombinant erythropoietin is relatively safe for home dialysis patients. A small number of patients successfully self-administered recombinant erythropoietin at home after only a brief explanatory session by their physician (110).

In another study of home patients whose target hematocrit level was attained and stabilized in the dialysis facility, a dose of 50 units/kg was used to maintain the hematocrit. Researchers in the study cautioned that blood pressure should be well-controlled and measured 3 times daily in patients that self-administer recombinant erythropoietin (171). The nature and extent of any adverse reactions were not reported, however. Another study compared the incidence of adverse reactions in 55 home hemodialysis patients who self-administered recombinant erythropoietin with 31 patients who received recombinant erythropoietin in a dialysis facility. At an average dose of 101 units/kg, 9 of the facility patients experienced seizures over 23 months, and at an average dose of 108 units/kg, 1 self-administration patient experienced a seizure. Data on differences among the patient groups, which may have accounted for different rates of adverse effects, were not given. In another study, 2 patients that self-administered recombinant erythropoietin subcutaneously had pain at the injection site (82). It thus appears that home use of recombinant erythropoietin is relatively safe, if a patient's hematocrit has been stabilized, and if patients are provided instructions on how to properly administer the product and monitor response.

Recombinant erythropoietin and Blood Transfusions

The use of recombinant erythropoietin to treat anemia associated with chronic renal failure may substantially reduce or obviate the need for periodic blood transfusions. One nephrologist has estimated that 25 percent of dialysis patients require periodic or intermittent blood transfusions to maintain an acceptable hematocrit level (57). Use of recombinant erythropoietin instead of blood transfusions has multiple benefits. Although now relatively low, the risk of contracting blood-borne infections, such as HIV and various types of hepatitis, can be further minimized. Measures adopted in recent years to limit the spread of HIV through the nation's blood supply have minimized the risk of contracting these viruses. In 1989, screening procedures for HIV antibodies have lowered the risk of post-transfusion HIV infection to between 1 in 40,000 and 1 in 250,000 per transfusion. Post-transfusion hepatitis B infection occurs at the rate of 1 per 2,000 transfusions, and the risk associated with non-A, non-B hepatitis (NANBH, some of which is hepatitis C) is approximately 1 in 125 transfusions. The incidence of NANBH should further decrease in the near future with the development of a NANBH assay (4).

Eliminating or reducing blood transfusions may also increase the number of dialysis patients who can become candidates for successful renal transplantation. The development of transfusion-induced antibodies is a major factor limiting dialysis patients from receiving kidney transplants (27). Eliminating or reducing the need for blood transfusions could eliminate the development of these antibodies. In the long term, given a sufficient supply of transplantable organs and patient preference for this treatment, Medicare ESRD expenditures could decrease since expenditures for dialysis patients are about three times as much as transplantation (45). Despite the high -initial costs of transplantation, lower costs of maintaining patients with functioning transplants implies that Medicare recovers the costs of transplantation in about 3 years. In addition, transplant patients tend to have a better quality of life than do dialysis patients.

Finally, the use of recombinant erythropoietin could decrease Medicare's expenditures for blood and blood products. It is not evident, however, if the use of recombinant erythropoietin as a substitute for blood will ultimately reduce expenditures for the Medicare program. Recombinant erythropoietin may actually cost Medicare more than blood transfusions. Medicare covers 80 percent of the cost of blood transfusions after a beneficiary has met a 3-pint deductible under Part B of the program. That is, the patient has to replace or pay for 3 pints of blood before the program covers the cost of blood. The cost of blood does not count toward the annual Part B deductible, currently $75. In addition, blood provided under Part B does not meet the 3-pint Part A deductible (42 CFR 410.161).

SUMMARY OF SAFETY AND EFFICACY OF RECOMBINANT erythropoietin

Recombinant erythropoietin administered intravenously produces a dose-dependent rise in hematocrit level and can reduce or eliminate the need for blood transfusions in patients with anemia associated with chronic renal failure. The number of patient reaching a target hematocrit also depends upon the dose. Current information suggests that greater than 90 percent of patients will reach a target hematocrit of 30 percent with a dose of 100 units/kg. Some patients will reach the target with lower doses.

Further studies need to be done to evaluate long-term side effects and outcomes of therapy based on age (e.g., the pediatric and elderly population), race (outcomes among the various racial groups), and other underlying disease states in chronic renal failure patients. The effect of recombinant erythropoietin on predialysis patients also needs to be explored, that is, does the use of the product in this group of patients have the potential to delay the need for dialysis or does it accelerate the rate of renal injury?

Although evidence suggests that subcutaneously administered recombinant erythropoietin is efficacious, additional studies are needed to determine whether lower doses may be used in lieu of currently recommended doses, and whether lower doses can minimize the incidence of adverse reactions.

Initial studies seem to indicate that the quality of life of dialysis patients maybe improved with recom-

binant erythropoietin; however, additional studies are being conducted to evaluate the long-term impact of recombinant erythropoietin on the quality of life. Many factors contribute to the quality of life of dialysis patients, including the symptoms of anemia and treatment for underlying disease states. In addition, dialysis patients are generally taking drugs for many of these underlying disease states, which may have side effects that negate any positive impact that can be attributable to recombinant erythropoietin. For example, lethargy and impotence are common adverse reactions to antihypertensive mediations. Studies also need to be done on recombinant erythropoietin's ability to allow dialysis patients to return to work. This factor may depend more on current financial incentives for the patients not to return to work than on their ability to work.

A notable number of patients developed hypertension during the course of clinical trials, a relatively manageable adverse reaction to recombinant erythropoietin. Seizures appear to be the most serious side effect, but the relative risk appears to be no higher in treated patients than untreated patients. This event may be related to the hypertensive state of the patient and the rate of increase in hematocrit. Available information does not indicate whether the occurrence of adverse reactions in treated vs. non-treated patients, including hypertension and seizures, is statistically significant. Hypertension and seizures may also be associated with chronic renal failure.

Although recombinant erythropoietin has been studied in patients since 1986, there are still a number of outstanding issues that need to be addressed related to dosing, side effects, and long-term effect on the quality of life. As additional patients receive the product over a longer period of time, and additional information is collected, clinicians will be better able to address these and other identifiable issues that relate to patient care.

INTRODUCTION

A therapeutic product, such as a biologic, becomes available in the health care marketplace after many years of developing and researching the product, testingit for safety and efficacy in humans and animals, gaining marketing approval from the Food and Drug Administration(FDA), and finally developing a process for distributing and marketing it to health care professionals and facilities.

This chapter describes the history of the development, production, and marketing of recombinant erythropoietin in the United States. A complex set of legal and regulatory forces are shaping the recombinant erythropoietin marketplace, including biotechnology patent issues, orphan product designations, and licensing agreements among the various manufacturers. Based on this information, this chapter discusses the supply side of the market for recombinant erythropoietin. The final sections of the chapter outline arrangements for distributing the biologic and discuss sources of demand for dialysis patients and others.

HISTORY OF DISCOVERY AND PRODUCTION

erythropoietin is an amino acid glycoprotein hormone that is produced by the kidneys and liver in humans and animals[1](102). Although the medical significance of erythropoietin has long been recognized, a process to produce sufficient quantities of pure erythropoietin for therapeutic purposes had eluded scientists for almost 80 years.

It was first postulated in 1906 that erythropoietin was the natural molecule responsible for the regulation and control of red blood cell production in the body (116,137). In 1957, it was discovered that erythropoietin was produced by the kidneys and that the anemia of chronic renal disease was caused, at least in part, by deficiency of this renal hormone (76).

Extended medical research on erythropoietin was minimal, however, because of its scarce availability from natural sources and the lack of a technique that could sufficiently purify the compound for human administration. Attempts to isolate and purify erythropoietin from various sources yielded unstable, biologically inactive preparations of the hormone.

Milestones in the development of recombinant erythropoietin are listed in table 3-1. A major breakthrough for the potential production of erythropoietin for therapeutic use occurred in 1977, when scientists developed a technique that isolated and highly purified erythropoietin from the urine of severely anemic patients (102). Although the purification technique itself did not provide sufficient material for therapeutic use, it lead to subsequent work using genetic engineering.

In the 1980s, several biotechnology manufacturers simultaneously pursued strategies to develop processes to produce recombinant erythropoietin for therapeutic use. These included Amgen Inc. of Thousand Oaks, California and Genetics Institute of Cambridge, Massachusetts.

Amgen and Genetics Institute utilized biotechnology to develop a process to produce recombinant erythropoietin for therapeutic use. Biotechnology is the application of biological systems to technical and industrial processes. It has been defined as any technique that uses living organisms or parts of living organisms to make or modify products, to improve plants or animals, or to develop microorganisms for specific use (148). Biotechnology is now commonly used by many industrial sectors, including plant agriculture, hazardous waste management, and human therapeutics. In the pharmaceutical field it can be substituted for conventional methods of making new therapeutic entities by cloning cells that produce human compounds and by producing large quantities of scarce compounds. Pharmaceuticals made through biotechnology are usually classified into one of three categories: those that affect the immune system, those that mediate human tissue repair, and those that correct metabolic defects or alter metab-

[1]Although the kidney is the major producer of exythropoietin, about 10-15 percent is produced by the liver (63).

Table 3-l-Milestones in the Development of Recombinant Erythropoietin

Date	Milestone
1977	Scientists discover a process that produce highly spurified erythropoietin, but a process for producing significant quantities of the compound is still unavailable.
1983	Amgen clones the gene for human erythropoietin.
1984	Amgen and Kirin Brewery of Japan enter into a licensing agreement for recombinant erythropoietin.
1984	Genetics Institute and Chugai Pharmaceuticals of Japan enter into a licensing agreement for erythropoietin.
Nov. 30, 1984	Amgen applies for patent covering its cell line that produces recombinant erythropoietin in Chinese hamster ovary (CHO) cells.
January 1985	Genetics Institute applies for patents covering erythropoietin and recombinant erythropoietin.
Sept. 30, 1985	Amgen and Ortho enter into licensing agreement for recombinant erythropoietin.
Oct. 8, 1985	Genetics Institute and Boehringer-Mannheim enter into a licensing agreement for recombinant erythropoietin in European markets.
April 1986	Amgen receives orphan drug designation for use of recombinant erythropoietin for anemia associated with ESRD.
June 30, 1987	Genetics Institute patent granted.
August 1987	Ortho receives orphan drug designation for use of recombinant erythropoietin for anemia associated with ESRD.
October 1987	Chugai Pharmaceuticals of Japan receives orphan drug designation for use of recombinant erythropoietin for anemia associated with ESRD.
Oct. 27,1987	Amgen's patent granted.
November 1987	Amgen files a PLA and ELA with the FDA for use of recombinant erythropoietin for anemia associated with ESRD.
May 17, 1988	Chugai Pharmaceuticals of Japan and Upjohn Company of Kalamazoo, Michigan form Chugai-Upjohn of Rosemont, Illinois.
July 1988	Ortho receives orphan drug designation for use of recombinant erythropoietin for anemia of preterm infancy.
September 1988	Chugai-Upjohn files a PLA and ELA with FDA for use of erythropoietin for anemia associated with chronic renal failure.
February 1989	Ortho files a PLA and ELA for use of recombinant erythropoietin for anemia associated with chronic renal failure and for infection or treatment of human immonodeficiency virus (HIV).
March 1989	Ortho receives orphan drug designation for use of recombinant erythropoietin for anemia associated with HIV infection or treatment.
June 1,1989	FDA approves Amgen's PLA and ELA for use of recombinant erythropoietin (Epoetin alfa) for anemia associated with chronic renal failure.
October 1989	FDA informs Amgen that it has 7 years of market exclusivity for use of Epoetin alfa in anemia of chronic renal failure (retroactive to June 1, 1989)[a].
December 1989	Boston court rules that central claims of Amgen's and Genetics Institute's recombinant erythropoietin patents are valid, and certain other parts are invalid.
March 15,1990	Boston court orders Genetics Institute and Amgen to submit royalty-free cross-licensing agreement to court within 60 days and resolve dispute over orphan product designations.

[a]Amgen originally filed a PLA for the use of recombinant erythropoietin in the anemia of End Stage Renal Disease (ESRD). At the request of the FDA, and prior to approval, this indication was expanded to chronic renal failure. The Office of Orphan Products Development then awarded orphan drug status to Amgen's Epoetin alfa for the broader indication of chronic renal failure (142).

KEY: ELA = establishment licensing application; PLA = product licensing application; ESRD = end stage renal disease.

SOURCE: Office of Technology Assessment, 1990.

olism unrelated to the immune system. Recombinant erythropoietin is classified as a recombinant product for tissue repair, since replacement of red blood cells is considered tissue regeneration (15).

The aspect of pharmaceutical biotechnology that Amgen used to make recombinant erythropoietin is genetic engineering, which is defined as the purposeful manipulation of an organism's deoxyribonucleic acid (DNA) or hereditary material.[2] Genetic engineering of recombinant erythropoietin is a multistage operation requiring identification of the gene that produces erythropoietin, isolation of the gene, replication of the gene in an easily manipulated microorganism, production of recombinant erythropoietin, and purification of recombinant erythropoietin in a stable, biologically active form (15). Large-scale production of recombinant erythropoietin was accomplished through insertion of the human erythropoietin gene into Chinese hamster ovary (CHO) cells, which were then able to produce recombinant erythropoietin (160).

Amgen entered into several licensing agreements with other pharmaceutical manufacturers for recombinant erythropoietin, as indicated in table 3-2.[3] For example, it licensed its recombinant erythropoietin rights in Japan to the Kirin Brewery in 1984. It also entered into a licensing agreement in 1985 with the Ortho Pharmaceutical Corporation, in Raritan, New Jersey, a subsidiary of Johnson and Johnson (166). Under the provisions of this agreement with Ortho, Amgen retained the U.S. marketing rights to recombinant erythropoietin for anemia associated with chronic renal failure in individuals requiring dialysis, and Ortho obtained recombinant erythropoietin marketing rights for all other indications in the United States, including anemia associated with chronic renal failure for individuals who do not yet require dialysis (predialysis). Ortho also gained the rights to all uses of recombinant erythropoietin in foreign markets other than Japan and China.[4]

Table 3-2-Recombinant erythropoietin Marketing Rights

Company holding patent	Region	Company holding distribution/ marketing rights
Amgen Inc.	USA (dialysis)	Amgen Inc.
	USA (non-dialysis)	Ortho Pharmaceutical
	Japan	Kirin Brewery
	Europe	Ortho Pharmaceutical
Genetics Institute	USA	Chugai-Upjohn
	Japan	Chugai Pharmaceuticals
	Europe	Boehringer-Manheim

SOURCE: Retterson, 1989 (117); Sobota, 1990 (132).

Building on the 1977 purification technique breakthrough, Genetics Institute developed a method for producing erythropoietin in 1984. Genetics Institute licensed its erythropoietin product rights to the Chugai Pharmaceutical Company in Japan and to the Boehringer-Mannheim Company in Europe (127). In order to sell recombinant erythropoietin in the United States, Chugai Pharmaceuticals of Japan entered into a cooperative marketing agreement in May 1988 with a major pharmaceutical manufacturer, the Upjohn Company of Kalamazoo, Michigan, to form the Chugai-Upjohn Company, based in Rosemont, Illinois (see table 3-2).

The next steps in bringing recombinant erythropoietin to market were for the manufacturers to test the safety and efficacy of the product in animals and humans and to submit the required data to FDA for approval to market the product.

2 DNA is the molecule in chromosomes that is the repository of genetic information in all organisms (with the exception of a small number of viruses in which the hereditary material is ribonucleic acid, known as RNA). The information coded by DNA determines the structure and function of an organism.

3 In the legal context, a license is written authority granted by the owner of a patent to another party empowering the latter to make or use the patented article for a limited period of time or in a limited territory (14). In a licensing agreement, a pharmaceutical manufacturer usually sells its rights to produce and market a product or specific uses of a product to another manufacturer in return for a fee and a royalty arrangement based on sales of the product.

4 In March 1990, Amgen and Ortho were involved in binding arbitration to settle disputes related to their 1985 licensing agreement.

FDA APPROVAL OF RECOMBINANT erythropoietin

In order for a prescription drug or biologic to be marketed in interstate commerce in the United States, it must have FDA approval. A biologic is defined as any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of humans (21 CFR 600.3h).

The FDA approval process for new therapeutic products, including biologics, involves a lengthy, complex, and rigorous series of tests for safety and efficacy (21 CFR 601.25dl). After tests in laboratory animals indicate that a compound may have therapeutic value in humans, three phases of clinical trials are required prior to FDA approval (21 CFR 312.21).

Phase I trials involve the participation of a small number of healthy volunteers or patients to determine the safety of the product and appropriate dosing ranges and intervals? The data obtained in this phase should be used to design well-controlled, scientifically valid studies in later phases. Phase II trials include controlled clinical studies that involve the participation of patients who have the disease the product is supposed to treat. The purpose of these studies is to determine the initial efficacy of the product, dosing parameters in diseased patients, and how the agent is metabolized and excreted by the human body. Phase III trials include a series of controlled and uncontrolled studies in which a total of several hundred to several thousand patients are administered the product to gather additional information about efficacy and safety. Phase III studies also determine whether the product produces a broader range of adverse effects than those detected in the smaller Phase I and II studies. An additional series of studies, known as Phase IV studies, may be undertaken after the product is marketed to determine long-term adverse effects that may not have been detected during the first three phases.

After the first three phases of clinical studies for a biologic are completed, the manufacturer submits a product Licensing Application (PLA) and Establishment Licensing Application (ELA) to the FDA. A biologic cannot be marketed unless a PLA and ELA are both approved by FDA. PLA approval is based on safety and efficacy data generated from the clinical trials. ELA approval is based on inspection and certification by FDA personnel that the facilities in which the biologic is to be produced are in compliance with FDA's definition of good manufacturing practices (21 CFR 601.10b).[6]

Amgen's PLA and ELA for the use of recombinant erythropoietin for anemia associated with end-stage renal disease (ESRD) were submitted to FDA in October 1987 and approved June 1, 1989.[7] FDA, however, approved the product for use in the broader population of chronic renal failure, of which ESRD is a subset.[8] The brand name for Amgen's product is Epogen.

Ortho submitted a PLA and ELA to FDA in February 1989 for recombinant erythropoietin for anemia associated with chronic renal failure and for the anemia associated with human immunodeficiency virus (HIV) infection and treatment (l). FDA has not yet approved either application. The brand name for Ortho's product is Eprex (174).

Chugai-Upjohn submitted a PLA and ELA for its recombinant erythropoietin in September 1988, and neither has yet been approved (l). Chugai-Upjohn is

5 The number of participants required for each phase of clinical trials depends on the numbers necessary to achieve sufficient statistical power.

6According to regulations, licenses for the maintenance of establishments for the manufacture and preparation of biologics may be issued only upon showing that the establishment and the products meet standards designed to ensure the continued safety, purity, and potency of the products (42 USC 201).

I An inspection of the Amgen production facility was conducted by the Center for Biologics Evaluation and Research on January 9-11,1989 (160).

8 FDA reasoned that ESRD is one phase along the continuum known as chronic renal failure, and that chronic renal failure is the more global term which adequately describes the spectrum of renal insufficiency. Patients who are being dialyzed and patients who are not being dialyzed may both be anemic and may require transfusions, and with the development of recombinant erythropoietin, may be candidates for treatment with the product (159).

seeking FDA-approval for the use of recombinant erythropoietin for anemia associated with chronic renal failure (l), and will use Marogen as the trade name for its product (132).

FDA developed a nomenclature to distinguish among the potential recombinant erythropoietin products of the various manufacturers. The term epoetin is to be used for recombinant erythropoietin, and a modifier, such as alfa, beta, gamma, etc., will be added to identify the products of the various manufacturers approved by the FDA (160). Therefore, since Amgen's recombinant erythropoietin was the first to be FDA approved, it is known as Epoetin alfa. The next manufacturer's product to be approved by the FDA, if any, would be known as Epoetin beta.[9]

RECOMBINANT erythropoietin AND PATENT DISPUTES

Under the applicable U.S. laws, a patent maybe issued to cover "any new useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." (35 USC 101). The patentability of new synthetic pharmaceutical entities is well established in the U.S. legal system. The patent is a major mechanism by which pharmaceutical manufacturers protect their investment in research and development. Prior to 1980, the U.S. patent office held that living organisms were products of nature and outside the scope of the office's statutory subject matter. Based on this reasoning, the office did not grant patents on such products (148). This situation changed with a 1980 landmark Supreme Court decision, Diamond vs. Charkabarty, in which the Court ruled that live, microorganisms made by humans were patentable (477 USC *303, 1980).*

Uncertainty surrounding the actual protection that a patent gives to biotechnology products continues to present potential barriers to further innovation and commercialization in this industry (148). The patent disputes that have developed among Amgen, Chugai, and Genetics Institute are an indication of the complexity and uncertainty of the biotechnology patent law field.

On October 27, 1987, Amgen received a patent on the intermediate product that is used to make recombinant erythropoietin in CHO cells. It applied for the patent on November 30, 1984.[10] Genetics Institute received a patent on homogeneous erythropoietin on June 30, 1987. It applied for the patent on January 11, 1985.[11] Also in January 1985, Genetics Institute filed for a patent on recombinant erythropoietin analogous to Amgen's. Amgen, Chugai, and Genetics Institute are all using recombinant technology to produce recombinant erythropoietin in Chinese hamster ovary cells (48).

In October 1987, in a suit filed against both Genetics Institute and Chugai Pharmaceutical, Amgen claimed that the companies were infringing on its recombinant erythropoietin patent. Genetics Institute and Chugai Pharmaceutical counter sued Amgen on the same grounds. In a complex decision, a Boston court ruled in December 1989 that certain claims of each patent were valid, but that other parts of each patent were invalid (6). The court concluded that each manufacturer was infringing on parts of the

9 According to the upcoming edition of the ***United States Adopted Names and the United States Pharmacopeia Dictionary of Drug Names,*** Amgen's product has been designated **Epoetin alfa** and Chugai-Upjohn's product **Epoetin** beta, notwithstanding the fact that, by April 1990, FDA had not officially given the designation of **Epoetin** beta to a specific manufacturer's product.

The FDA generally relies on **USAN** to adopt names for new chemical entities and biological products. **USAN** is a private organization sponsored by the USP, American Medical Association, and American Pharmaceutical Association and has been engaged in the assignment of names to drugs since January 1964. According to regulations, however, FDA retains the right to publish official names of drugs in situations in which the **USAN** or other official common name is unduly complex or is not useful for another reason, or two or more official names have been applied to a single drug, or to two or more drugs that are identical in chemical structure or pharmacological action and that are substantially identical in strength, quality, or purity (21 CFR **299c).** It appears, therefore, that FDA will make the final determinations of names for recombinant erythropoietin products.

10 **Amgen's** patent is No. 4,703,008, "DNA Sequencing Encoding erythropoietin." U.S. Patent Office Application No. 675,298.

11 Genetics Institute's Patent is No. 4,677,195, "Homogeneous erythropoietin." U.S. Patent Office Application No. 690,8S3.

other manufacturer's patent. Genetics Institute, which was producing recombinant erythropoietin in the United States for sale in Europe, was infringing on Amgen's patent, and Amgen, which was producing recombinant erythropoietin for sale in the United States, was infringing on Genetics Institute's patent. Because Chugai was producing recombinant erythropoietin in Japan, however, it was not infringing on Amgen's recombinant erythropoietin patent. According to the court, U.S. patent protection for Amgen's intermediate product does not extend to production of recombinant erythropoietin by another manufacturer in a foreign country. If Amgen had a patent on the process by which it produced recombinant erythropoietin, or a patent on recombinant erythropoietin itself, then the court might have ruled differently.

The issue of whether U.S. patent protection on intermediate products extends to production outside the United States had been raised in another dispute between Amgen and Chugai. In January 1988, Amgen asked the U.S. International Trade Commission (ITC) to block Chugai Pharmaceutical from importing recombinant erythropoietin from Japan on the grounds that Chugai Pharmaceutical was infringing Amgen's U.S. patent. Chugai Pharmaceutical was making recombinant erythropoietin by a process similar to Amgen's and importing it from its Japanese production facilities for use in U.S. clinical trials (165).

In January 1989, the ITC held that its jurisdiction did not cover the use of a patented product abroad (165). Although Chugai Pharmaceuticals indeed utilized a process similar to Amgen's in the production of Chugai's product, Amgen had a patent on one ingredient that was essential to making recombinant erythropoietin, not on the process by which it was produced. Therefore, Chugai Pharmaceutical could sell recombinant erythropoietin in the United States once it had an approved PLA and ELA for its facility in Japan from FDA, even if Chugai Pharmaceutical was making the product by a process that used Amgen's patented host cells. If Chugai produced recombinant erythropoietin in Japan by a process that Amgen patented in the United States and attempted to market it here, however, it would indeed constitute patent infringement.

Some analysts have speculated that a cross-licensing agreement between the two manufacturers will result from this decision (136). Cross-licensing is the exchange of licenses by two or more patent holders in order that each may use or benefit from the patents of the other (14). Cross-licensing could enable both Amgen to remain on the market and Chugai-Upjohn to enter and remain on the market.

On March 14, 1990, a Federal court judge in Boston ordered Amgen and Genetics Institute to submit to the court a royalty-free cross-licensing agreement with 60 days. The judge indicated that he would issue an injunction to prevent the manufacturer who was noncompliant with his order from making and selling recombinant erythropoietin in the United States (168). The judge indicated that the orphan product status of the manufacturers' products should also be resolved in the agreement (7).

These circumstances surrounding the issuance of two patents on recombinant erythropoietin products are examples of the evolving nature of this body of law. It appears, however, that the granting of two patents will result in multiple sources of recombinant erythropoietin.

RECOMBINANT erythropoietin AND THE ORPHAN DRUG ACT

The Orphan Drug Act of 1983 (Public Law 97-414) provides economic incentives for pharmaceutical manufacturers (sponsors) to research, develop, and market products for rare conditions. The term rare disease or condition was defined in a 1984 amendment to the Act (Public Law 98-551) as any disease or condition that 1) affects fewer than 200,000 persons in the United States or 2) affects more than 200,000 persons in the United States and for which no reasonable expectation exists that the cost of developing and making available in the United States a drug for such a disease or condition will be recovered from sales.

FDA's awarding of orphan status to a particular sponsor's product is made independently of FDA's approving the product. Before it submits a PLA to the FDA, a sponsor must apply for orphan product status to the Office of Orphan Products Development (69). Several sponsors may obtain orphan

product status for the use of a particular product for a particular condition; however, only that sponsor that receives FDA approval first receives 7 years of marketing exclusivity for that product for that condition. Although regulations to implement the Orphan Drug Act have yet to be put in final form, the Office of Orphan Products Development has been operating within the following guidelines in granting orphan product designations.

Several pharmaceutical manufacturers may obtain orphan product designations for a product's use for a particular condition. Only the sponsor whose product FDA approves for marketing first, however, is awarded the 7-year market exclusivity for that product for the approved use. FDA may grant market exclusivity to two versions of the same product if each applies for a different rare condition. In addition, FDA may grant market exclusivity to two products for the same condition, if FDA considers them different products (69).

For the purpose of orphan product designation, a sponsor makes the estimate of the patient population at the time of submission of the application, and the Office of Orphan Products Development reviews the sponsor's estimate. The Act does not currently permit FDA to remove an orphan product designation if the patient population subsequently exceeds *200,000.* Marketing exclusivity may be removed, however, if the manufacturer falsified claims in making application for the designation or is unable to produce sufficient quantities of the product for the patient population.

Amgen, Ortho, and Chugai all have orphan drug designations for the use of recombinant erythropoietin in various medical conditions (see table 3-3). Since Amgen's recombinant erythropoietin was the first to be approved by FDA, it was designated Epoetin alfa and has market exclusivity for chronic renal failure.[12]

Ortho's product has received orphan designation for anemia associated with ESRD, HIV, and infant prematurity, and Chugai's has received orphan designation for anemia associated with ESRD. Regardless of FDA's decision about whether other companies' products are different from Amgen's, if Ortho's Eprex obtains FDA approval for anemia associated with HIV or infant prematurity, Ortho could receive 7 years of marketing exclusivity for the

IL Amgen's original orphan product designation was for anemia associated with ESRD. After FDA approved Epoetin alfa for the broader indication of chronic renal failure, the orphan product designation and market exclusivity were expanded to reflect this broadened indication (142).

Table 3-3--Recombinant erythropoietin Products with Orphan Drug Designations, March 1990

Orphan condition	Sponsor holding designation	PLA and ELA filed	Status
Anemia of ESRD	Amgen (Epogen, Epoetin alfa)[a]	11/87	approved, 6/89
	Ortho (Eprex)	2/89	pending
	Chugai Pharmaceutical (Marogen)	9/88	pending
	McDonnell-Douglas		suspended
	Organon-Teknika		suspended
Anemia of HIV	Ortho (Eprex)	2/89	pending
Anemia of infant prematurity	Ortho (Eprex)		clinical trials

a Amgen's orphan product designation is for use of recombinant erythropoietin for anemia associated with chronic renal failure (142).

KEY: ELA = establishment licensing application; ESRD = end-stage renal disease; HIV = human immunodeficiency virus; PLA = product licensing application.

SOURCES: Turner, 1990 (142); US DHHS, FDA, 1989 (161); 54 CFR 16295, April 21, 1989.

approved indication, because the same product may have orphan status for different rare conditions. By April 1990, FDA had not determined whether Chugai's or Ortho's product is different from Amgen's. If FDA finds either product structurally different from Amgen's, that company's product could theoretically be granted 7 years' exclusivity for anemia associated with ESRD or chronic renal failure. FDA had not decided by April 1990 whether the broader indication of chronic renal failure rather than ESRD would be granted to Ortho's or Chugai's product, if either was deemed different from Amgen's, was given FDA approval for the same indication, and was granted market exclusivity (142). Thus, independently of the resolution of legal disputes among the companies, FDA's decisions regarding product differentiation and market exclusivity have the potential to affect the number of companies in the U.S. market and the indications for which they may market recombinant erythropoietin.

THE SUPPLY SIDE OF THE MARKET FOR RECOMBINANT erythropoietin

Since the FDA approved Epogen in June 1989, Amgen has been the sole supplier of recombinant erythropoietin for the U.S. market. Although Amgen has held a monopoly on the U.S. sale of this biologic, certain factors have limited its market power. In the short term, Amgen has faced the Medicare program as the dominant payer of recombinant erythropoietin. Not only does Medicare command substantial leverage because of its coverage of dialysis patients, but also Amgen has been particularly dependent on Medicare revenue because Epogen is the company's first and so far its only product on the market.

The dynamics of this market also promise to limit Amgen's influence. Given developments in the legal and regulatory arenas, it is possible that in the near future, the United States will have two additional sources of recombinant erythropoietin: Ortho's Eprex and Chugai-Upjohn's Marogen. This situation illustrates several possible sources besides clinical significance from which products may draw market power: patents, exclusivity as an orphan product, agreements to divide the market among competitors, FDA approval for certain medical indications, and other differentiation from competing products.

The very purpose of a patent is to encourage innovation by granting new products a period free from competition. For products developed through biotechnology, this period of patent-protected monopoly power appears to be shorter than for other products. In the ease of recombinant erythropoietin, Amgen and Genetics Institute have been challenging each other's patents. Unable to resolve the dispute through negotiation, the parties face a court order to reach an agreement to cross-license their rights without payment of royalties. Although attention has focussed on U.S. patents, the scope is properly international, with patents in Japan and Europe relevant to the overall package.

The court order also charges the companies to address another source of market power, FDA's grant of 7 years' exclusivity to an orphan product. Similar to patents, this period of market exclusivity was intended to protect orphan products from competitors and thereby to stimulate the development and testing of products for rare medical conditions. Controversy surrounds the appropriate scope of the condition considered rare and the estimate of the population afflicted. Thus, Chugai disputes the validity of the exclusivity granted to Amgen's Epogen, and Amgen opposes FDA's granting Chugai's Marogen exclusivity. Even more basic is the advisability of granting exclusivity to a product that two or more companies are developing for the same condition. In the case of human growth hormone, FDA's grant of exclusivity to more than one company, on the grounds that different structures rendered the products different entities, has allowed competitors to enter the market (10).

Both Amgen and Genetics Institute have used licensing agreements with other firms to segment the market, both domestic and international. These agreements may divide the market by medical indication, such as Amgen's retaining rights to the U.S. dialysis market and licensing rights to the predialysis population to Ortho. Or companies may

divide the market geographically, such as Genetics Institute's licensing of Boehringer-Mannheim for the European market. Especially agreements pertaining to different medical indications may prove difficult to enforce. As described below, physicians may prescribe different brands interchangeably.

FDA approval of a product for certain conditions offers another related route to gain market power. FDA approval allows a manufacturer to segment the market, since a company may promote its product only for approved indications. Ortho's Eprex has applied for approval for anemia associated with HIV and with chronic renal failure.

Like the other bases of market power, this one is also subject to encroachment. Chugai, for example, has applied for approval for anemia associated with end-stage renal disease, a medical condition that is a subset of Amgen's approved indication, anemia of chronic renal failure. Perhaps even more telling, the indications for which FDA approves different brands of recombinant erythropoietin are unlikely to restrict their clinical uses. Although FDA approves a product only for a specific indication, physicians and other providers may use it for a different indication, especially if there are economic incentives and it is clinically efficacious to do so. For example, even if Eprex becomes the only brand approved for anemia associated with HIV, physicians may prescribe Epogen or Marogen for the condition. Similarly, it may become common practice for physicians to use recombinant erythropoietin to increase autologous blood donations or to treat anemia associated with cancer therapy even before FDA approves these indications. To the extent that physicians do not restrict their use of a particular brand of recombinant erythropoietin to the indication for which it was approved, any market power that brand may have derived from FDA approval for a specific indication will be eroded.

A product may also gain market power through other methods of differentiating itself from competitors, such as by physical characteristics or through brand loyalty. By catering to the needs of different users, manufacturers attempt to segment the market and thus support higher prices and gain greater revenue. This is an effective strategy for increasing profits only to the extent that it outweighs the advantages of serving a larger share of the market. Manufacturers of recombinant erythropoietin are already adding features to differentiate their products, such as Marogen's use of a powder in contrast to the liquid form of Epogen and Eprex. Manufacturers may vary the volumes of the product's containers; some buyers may prefer large containers and others small.

Promotional activities may seek to gain a larger market share and users' commitment to a certain brand. As the first brand on the market, Epogen may acquire brand loyalty independent of Amgen's promotional activities. Brand loyalty, however, can be eroded with price concessions and other benefits offered by competing brands.

DISTRIBUTION OF RECOMBINANT erythropoietin

Recombinant erythropoietin is currently provided to patients in dialysis facilities (hospital-based or free-standing) and physicians' offices. If FDA-approved indications increase beyond chronic renal disease and if legislation is enacted to allow Medicare coverage for self-administration of this biologic, then pharmacies and dialysis distributors (when serving home dialysis patients) may also become providers. Providers share the common functions of administering or dispensing recombinant erythropoietin to patients and submitting claims to Medicare carriers or fiscal intermediaries, but only physicians and dialysis facilities make decisions about use.

Although manufacturers, wholesalers, and other intermediate suppliers may distribute recombinant erythropoietin to providers, Amgen has been selling only to wholesalers, not directly to providers. Intermediate suppliers include wholesalers, dialysis distributors (when serving dialysis facilities), pharmacies (when serving physicians), and other suppliers to physicians. Dialysis distributors specialize in equipment and other supplies relating to dialysis. Physician suppliers also deal in a wide range of products. Unlike providers, manufacturers and intermediate suppliers do not deal directly with patients and are not responsible for billing Medicare. Although

the unit cost of recombinant erythropoietin to each provider is equal to the sum of the manufacturer's price and the intermediate supplier's markup, the manufacturer's price is by far the larger component.

Chains of dialysis facilities maybe large enough purchasers to bypass intermediate suppliers and obtain a product such as recombinant erythropoietin directly from the manufacturer. smaller organizations are by far more likely to purchase products through wholesalers or dialysis distributors. Hospital pharmacies, which often jointly purchase through a buying group that deals with pharmaceutical wholesalers or directly with manufacturers, usually supply hospital-based dialysis facilities. Physician providers often obtain products from physician suppliers or pharmacies. Independent pharmacies would be likely to obtain a product such as recombinant erythropoietin from wholesalers, whereas large chains might purchase it directly from the manufacturer. Dialysis distributors would obtain the product either from manufacturers or pharmaceutical wholesalers.

Medicare beneficiaries now receive recombinant erythropoietin primarily from dialysis facilities and also from physicians' offices. If legislation is enacted enabling Medicare to cover the self-administration of recombinant erythropoietin, many home dialysis patients may choose that alternative. Home dialysis patients could obtain recombinant erythropoietin from dialysis facilities, dialysis distributors, or, if new arrangements were made, from physicians' offices or pharmacies (see ch. 4 for current policies). If self-administration was covered, Medicare beneficiaries in the predialysis phase of chronic renal failure or with future medical conditions that might be approved could also obtain recombinant erythropoietin from physicians' offices or from pharmacies.

THE DEMAND SIDE OF THE MARKET FOR RECOMBINANT erythropoietin

At present, Medicare is by far the dominant payer for recombinant erythropoietin therapy. If FDA grants approval for indications besides anemia associated with chronic renal failure, Medicare's leverage in the market will probably diminish, as other payers become more prominent. In addition to Medicare, other Federal Government programs or agencies, such as Medicaid and the Departments of Veterans Affairs and Defense, also purchase or pay for recombinant erythropoietin. If Medicare acted in concert with these other Federal programs or agencies, its market leverage would be reinforced.

Estimates of the patient populations that might use recombinant erythropoietin range widely. According to most estimates of current patients, dialysis patients who are anemic comprise the largest group, with estimates from about 59,000 in 1984 to about 92,000 in 1990 (see table 3-4) (69,103,156).

The great variation in estimates of anemic patients in the predialysis phase of chronic renal failure reflects uncertainty about the number in the predialysis phase and about the proportion who are anemic.[13] Estimates of people in the predialysis phase range from 71,000-110,000 (174) to 93,000 (164), to somewhat over 230,000 (68), to over 2 million (41). Applying estimates of the percentage of people who are anemic to these figures yields, respectively, 9,000-18,600 (10-20 percent anemic) (51,164), 23,400 (10 percent) (68), 31,200-48,400 (44 percent) (174), and 740,000 (35 percent) (29) (see table 3-4).

Although information is not available to assess fully these estimates, it is likely that the estimate of the predialysis population, made by the Degge Group, Ltd., for Chugai-Upjohn, is too high. For example, the numbers of individuals with different comorbidities were summed to derive an estimate of the total symptomatic predialysis population. Since individuals are likely to have more than one of these comorbidities, summing numbers for each comorbidity will overstate the total. This factor, however, does not fully explain the large difference between the Degge Group's estimate and the other estimates. For example, according to the Degge Group's study, the largest comorbidity, diabetic nephropathy, comprised an estimated 1.4 million people. If only these people are considered and if a more conservative 20 percent rather than 35 percent are assumed to be

13 As for dialysis patients, not all predialysis patients who are anemic may be candidates for recombinant erythropoietin therapy (see ch. 2).

Table 3-4-Estimates of Individuals With Selected Conditions Who Are Anemic

Condition	Range of Estimates		
	Low	Medium	High
Dialysis Patients	58,900[a]		92,000[b]
Predialysis Chronic Renal Failure	9,000-18,600[c]	23,400[d] 31,200-48,400[e]	740,000[f]
AIDS	17,000[g]		

[a]Based on a 1984 estimate of dialysis patients submitted by Amgen to FDA (69) and an estimate that 75 percent of them are anemic, which was calculated from 1989 hematocrit level distributions obtained from National Medical Care, Inc. (103).
[b]An estimate of the total dialysis population was derived by projecting Medicare dialysis patients, who constitute about 93 percent of the total, to 1990 (46) and adding the remaining 7 percent, who are non-Medicare patients (156). The estimate othat 75 percent of the total are anemic was based on 1989 hematocrit distributions from National Medical Care, Inc. (103).
[c]Estimate of predialysis population from the National Center for Health Statistics (NCHS) (164) and estimate of 10-20 percent of predialysis population as anemic by Eschbach (51). The NCHS figure, 93,000, was based on 1983 discharges from short-stay nonfederal hospitals for whom chronic renal failure, ICD-9-CM Code 585, was listed as a diagnosis. It should be noted that an individual with chronic renal failure may have multiple hospitalizations in a given year, and individuals with this condition who were not hospitalized were excluded.
[d]Estimate of about 230,000 predialysis patients of whom 10 percent were estimated to be anemic (68).
[e]Based on estimates from a survey of randomly selected nephrologists before recombinant erythropoietin was approved: 71,000-110,000 predialysis patients of whom 44 percent had symptomatic anemia. Of these 44 percent, respondents thought 40 percent would be candidates for the biologic (174).
[f]Based on an estimate of over 2 million individuals with symptomatic chronic renal failure who are predialysis (41) and an estimate that 35 percent are anemic (132). The number of individuals with symptomatic chronic renal failure was based on prevalence estimates for this condition among the several comorbidities with which it is commonly associated. The percent anemic was based on an estimate of those with the condition who have a blood hemoglobin less than 10 g/all or hematocrit less than 30.
[g]calculated from an estimate of people living with AIDS in January 1990 (158) and the percent of these likely to become anemic subsequent to zidovudine use (119).

SOURCE: Office of Technology Assessment, 1990.

Table 3-5-Projections of Medicare-Eligible Dialysis Patients Who Are Candidates for Treatment With Recombinant erythropoietin by Age Group, 1990-1995[a]

Age group	1990	1991	1992	1993	1994	1995
0-14	607	605	600	593	583	572
15-24	3,021	3,135	3,224	3,291	3,335	3,357
2.5-34	7,385	7,401	7,347	7,230	7,059	6,837
3544	11,126	11,786	12,434	13,059	13,652	14,203
45-54	13,470	14,624	15,867	17,180	18$41	19,932
55-64	19,421	20,715	22,100	23,543	25,011	26,476
65-74	19,717	20,927	22,232	23,588	24,957	26,303
> 75	10,789	11,860	13,052	14,333	15,673	17,042
TOTAL	85,536	91,053	%,856	102,817	108,811	114,722

[a]Based on current treatment guidelines to use recombinant erythropoietin for a hematocrit of less than 30 percent.

SOURCE: Office of Technology Assessment, 1990. Based on data obtained from Eggers, 1989 (46) and National Medical Care, 1989 (103).

anemic, the estimate would still be relatively high, 280,000. There is some question, however, about the number of people with diabetic nephropathy who have symptomatic chronic renal failure. Although the Degge Group assumed that, overall, 22 percent of those with diabetic nephropathy have chronic renal failure, estimates cited in the literature start at 10 percent (41).

FDA is reviewing Ortho's PLA for anemia associated with HIV and, specifically for anemia associated with treatment with zidovudine. In January 1990, people living with acquired immunodeficiency syndrome (AIDS) numbered about 50,000 (158). Compared with untreated AIDS patients, about 34 percent more AIDS patients treated with zidovudine at 1,500 mg daily experienced a 25-percent or greater decline in hemoglobin levels from an initial level of 9.5 g/all or higher (119). About 17,000 people with AIDS could thus be candidates for recombinant erythropoietin. Although this figure is probably an underestimate of people infected with HIV who would be candidates for recombinant erythropoietin, it is difficult to estimate this population as well. About 12 percent of people with AIDS-related complex had similar declines in hemoglobin levels from zidovudine treatment. FDA has recently approved zidovudine for infected people with CD4-cell counts below 500, even if they are asymptomatic (163). But people earlier in the progression of disease have been less likely to develop anemia from treatment. Moreover, the recommended dose of zidovudine has been greatly reduced, from 1,200 mg to 500-600 mg daily (24, 162). Over time, as the HIV epidemic progresses, the population infected with HIV and those who develop AIDS will increase, but lower doses of zidovudine may reduce the likelihood that treated patients will develop anemia and use recombinant erythropoietin. Development of an effective and safe therapy for HIV infection that does not induce anemia would also lower the potential use of recombinant erythropoietin among this population.

Although Medicare expenditures for recombinant erythropoietin will most likely continue to increase, over time Medicare's share of the U.S. market will undoubtedly decline. Besides growth in Medicare's ESRD population, Medicare's share of the market in future years depends on FDA approval of additional indications, the sizes of the additional population, the proportions of these populations that are Medicare beneficiaries, and the extent to which other third-party payers cover recombinant erythropoietin.

Only for Medicare's dialysis population were data sufficient to make projections for future years. Future estimates of Medicare dialysis patients depend on several factors: the number of patients who initiate treatment in any one year; the number of patients who have a successful kidney transplant in each year and no longer need dialysis; the number in each year who have a failed transplant and must return to dialysis; and the number of patients on dialysis who die. Using these factors, Eggers developed a model that projects the number of total ESRD, dialysis, and transplant patients to the year 2000 (46). For each projection year, a low, midline, and high estimate of each population component was provided. OTA used Eggers midline projections of the dialysis component, to the year 1995, to estimate the number of beneficiaries on dialysis who will be candidates for treatment with recombinant erythropoietin (see table 3-5).

The calculations in table 3-5 assume that all dialysis patients with a hematocrit level of less than 30 will be eligible for treatment. The proportions, by age group, of dialysis patients with hematocrits below 30 were obtained from National Medical Care (NMC), the largest chain of U.S. dialysis facilities (11). These proportions were applied to Eggers' projections to generate the estimates in table 3-5. The information from NMC pertained to the largest Medicare beneficiary and patient group for which data were available; NMC treats about 20 percent of Medicare dialysis patients and operates in over 30 States (11). There is no reason to expect that the prevalence of anemia as an underlying condition in dialysis patients will change, although use of recombinant erythropoietin during the predialysis phase may increase the average hematocrit level of patients starting dialysis.

The estimates in table **3-5** understate total Medicare beneficiaries who may be candidates for recombinant erythropoietin through 1995. These estimates include neither beneficiaries in the predialysis phase nor those with other indications that might be approved by FDA.

INTRODUCTION

Since 1973, Medicare has paid for the medical and related services for over 90 percent of the U.S. population with End Stage Renal Disease (ESRD) (147). The ESRD program has become costly for Medicare. Expenditures have increased from $228 million in 1974 to an estimated $2.7 billion in 1989 (156). After a dialysis patient has met the annual Medicare Part B deductible, either through payment for dialysis or other covered medical services, Medicare pays 80 percent of the cost of medical services, and the patient pays 20 percent. This chapter describes Medicare's payment policies for various products and services provided to ESRD patients, pharmaceuticals provided in different settings, and recombinant erythropoietin itself. This background information provides the basis for the analysis in chapter 1 of payment options for recombinant erythropoietin.

MEDICARE PAYMENT POLICIES FOR ESRD SERVICES

Provisions for Medicare coverage and payment for ESRD services were enacted in the Social Security Amendments of 1972 (Public Law 92-603, Sec. 2991). Congress provided that individuals with ESRD, that is, permanent chronic kidney disease requiring continuous dialysis or a kidney transplant to maintain life, were deemed to be disabled and entitled to Medicare coverage regardless of their age, social status, or ability to pay (42 USC 246(l)(a)).

In 1988, 93 percent of the approximately 105,958 U.S. dialysis patients were approved for Medicare coverage or had Medicare coverage pending (156) (see table 4-l). Medicare coverage for dialysis patients generally begins in the third month after the month in which a regular course of dialysis is initiated (42 CFR 426(l)(a).

ESRD patients are served by 1,915 kidney transplant and dialysis centers, as listed in table 4-2. The majority of these providers are dialysis facilities, of which 63 percent are independent facilities and 37 percent are hospital based (156). The other 214 providers are kidney transplant facilities.

Table 4-l-Coverage for Dialysis-Related Medical Services in the United States, December 31, 1988

Coverage	Number of patients covered	Percent of patients covered
Total Medicare	98,191	92.6
(Medicare approved	91,820	86.6)
(Medicare Pending	6,371	6.0)
Department of Veterans Affairs..	3,722[b]	3.5
Other[c]	4,045	3.9
Total U.S. dialysis population	105,958	100.0

[a]Medicare coverage begins the third month after the month in which the course of maintenance dialysis treatments begin. Medicare coverage may begin in the first month of dialysis if the patient participates in a self-dialysis training program in a Medicare-approved training facility. The Medicare-pending category includes those patients that have applied for and are satisfying the three-month waiting period before dialysis benefits begin (42 CFR 426-lb).

[b]Department of Veterans Affairs (VA) dialysis patients include 3,132 in-unit or home dialysis patients who are affiliated with VA facilities and 590 patients who receive dialysis in Medicare-approved dialysis facilities for which VA makes payment to HCFA (109).

[c]Includes patients covered by Medicaid, private insurance (including those who have employer group health insurance coverage for the first year of ESRD, with Medicare's becoming the primary insurer after the first year), foreign nationals, and individuals who do not have coverage for services. HCFA does not collect separate data on Medicaid coverage of ESRD (123).

SOURCES: Otchin, 1990 (109); US DHHS, HCFA, 1989 (156).

Table 4-2--Dialysis and Kidney Transplant Service Providers in the United States, November 1989[a]

Type of provider	Number of providers
Total providers	1,915
Total kidney transplant providers	214
Total dialysis providers	1,807
Hospital-based dialysis	661
Independent dialysis	1,146
Inpatient dialysis	58

[a]Because some facilities fall into more than one classification, the sum of the individual classifications may exceed the total approved facilities.

SOURCE: US DHHS, HCFA, 1989 (156).

In general, a patient's dialysis facility furnishes a package of services, equipment, and supplies, including laboratory tests and certain drugs, for each dialysis treatment. Items and services in the package include bicarbonate dialysate, catheter changes, shunt declotting, cardiac monitoring, suture removal, surgical dressing changes, oxygen and its administration, and staff time involved in the administration of blood and certain parenteral[1] items (151).

Medicare pays for this package of dialysis services by a composite rate. The composite rate per dialysis treatment, which currently averages $129 for the hospital-based facilities and $125 for independent dialysis facilities, (151) must be accepted as payment in full by the facilities for all covered items and services.[2] The rate is based on a formula that takes into account the mix of patients that receive dialysis at a facility or at home and the relative cost of providing such services in these settings (Public Law 101-239).

Patients that receive dialysis at home may choose one of two payment methods. Under Method I, the dialysis facility is paid and must accept the composite rate as payment in full for providing all services, equipment, and supplies needed for home dialysis. Approximately 64 percent of all home dialysis patients chose Method I in 1988 (124). Under Method II, the patient may deal directly with a supplier to obtain home dialysis equipment and supplies. In 1988, 36 percent of all home dialysis patients chose Method II (124). Under a provision of the Omnibus Budget Reconciliation Act of 1989 (Public Law 101-239) that took effect Feb. 1, 1990, providers of supplies and equipment to home dialysis patients must also accept the composite rate as payment in full. Previously, reimbursement to suppliers under Method II was calculated on a reasonable charge basis, and suppliers could charge home dialysis patients more than the composite rate. This situation could result in higher cost-sharing for those home dialysis patients who chose Method 11.[3] In addition, all home dialysis patients must now be affiliated with a dialysis facility, whether they receive their home dialysis equipment and supplies from a facility or a supplier (Public Law 101-239). Medicare pays dialysis facilities and suppliers for services not covered under the composite rate according to a fee schedule (126).

Medicare pays for all dialysis-related physician services through a monthly per-patient payment, currently an average $173 (126). The physician, known as the patient's "capitated physician," receives the same amount whether the patient the physician supervises receives dialysis in a facility or at home.

ESRD patients cannot become members of health maintenance organizations (HMOs) or other competitive medical plans (CMPs) that have a risk-sharing contract to serve Medicare beneficiaries.[4] Beneficiaries may retain CMP membership if they develop ESRD subsequent to enrollment. For ESRD patients who are CMP members, Medicare pays a monthly prospective per-capita amount that covers both ESRD and non-ESRD services. Payment is based on the estimated amount (the average adjusted per capita cost)[5] that would be paid for Medicare-covered services if beneficiaries were not enrolled in HMOs and received care from local fee-for-service providers. The rates are adjusted for factors such as age, sex, disability, and, if available and appropriate, welfare and institutional factors (145).

ESRD networks, which function like peer review organizations (PROS) review the quality of care provided to dialysis patients. Under contract to the

1 **Parenteral** refers to some means, other than through the alimentary canal, to introduce a substance into the body. In this case, it refers to intravenous administration of certain drugs.

2 Each facility has its own composite rate, composed of a labor and non-labor portion. To determine a facility's actual payment rate, the labor portion of the appropriate base rate is first adjusted by an area wage index and then added to a **nonlabor** portion (154).

3 **An** exception is that for home patients on Continuous Cycling Peritoneal Dialysis **(CCPD),** Medicare may pay up to 130 percent of the median composite rate for hospital-based facilities (Public **Law** 101-239).

4 In a risk-sharing arrangement, a fiscal intermediary, such as an HMO or other **CMP,** assumes the financial risk of arranging for or providing care to Medicare enrollees (145).

5 See app. D for a definition of average adjusted per capita cost.

Health Care Financing Administration (HCFA), these 17 networks are generally organizations of nephrologists. During each year, the networks select approximately 12 percent of all dialysis patients to review quality-of-care problems. Each network develops its own criteria to assess the quality of care. The networks, which have some limited ability to impose sanctions on providers if problems are detected, do not have the ability to deny payment for claims. In March 1990, some of the networks initiated their own review of various aspects of recombinant erythropoietin use. HCFA has no immediate future plans to require the networks to review whether recombinant erythropoietin is being used appropriately in dialysis patients (99).

Payment for dialysis service claims is made by Medicare contractors. These contractors include intermediaries, which usually process claims for Part A providers, such as hospitals and dialysis facilities; and carriers, which process claims for Part B providers, such as physicians (20). These contractors, typically Blue Cross plans or commercial insurance firms, determine reasonable costs or charges for covered services, make payments, and guard against unnecessary use of Medicare-covered services.

MEDICARE'S PAYMENT POLICIES FOR PHARMACEUTICALS

General Payment Policies

HCFA first decides if a pharmaceutical (a drug or biological) should be covered by the Medicare program and then determines how payment should be made. Coverage and payment rules differ for each Medicare program, depending on whether the pharmaceutical is provided to an inpatient or outpatient.

HCFA's policy is that a pharmaceutical is covered for FDA-approved indications, unless HCFA determines that it is not safe and effective for a particular use or unless it is subject to a specific exclusion, such as self-administered pharmaceuticals, as discussed below. A HCFA contractor may cover and pay for an FDA-approved pharmaceutical for an indication for which there is no FDA approval, if it is documented in the medical literature that the pharmaceutical is commonly used in medical practice to treat that particular condition. These are commonly referred to as off-label uses. HCFA does not pay for the use of investigational pharmaceuticals, except in the case of some cancer agents. When HCFA views a coverage or payment issue to be significant, or contractors' interpretations of FDA actions differ, HCFA may issue specific national guidelines on the coverage status of a particular pharmaceutical (35).

In conjunction with its decision about coverage, HCFA also determines the amount that the program will pay for a particular pharmaceutical. The payment method is based on the setting in which the product is administered.

Under Part A, Medicare pays for the operating expenses associated with inpatient care for a particular diagnosis for the entire length of stay through freed rates set in advance, known as diagnosis-related groups (DRGs). DRGs classify patients according to primary diagnosis, the principal surgical procedure, and the type of discharge. Variations in the DRG rates paid to hospitals are a function of location (urban versus rural), area wage rates, a hospital's teaching affiliation, and the proportion of low-income patients served. Hospitals are paid these rates regardless of the costs that they actually incur (35). The facilities earn a profit when their costs fall below the payment and absorb the loss when the costs are higher than the payment. Payment for pharmaceuticals used during an inpatient stay are included in the predetermined DRG rate.

In accordance with the Social Security Act, Medicare Part B covers pharmaceuticals, if they cannot be self-administered by the patient, such as injectable; are reasonable and necessary for the diagnosis or treatment of an illness by a physician; or are provided incidental to a physician's service (Social Security Act 1861 (s)(2)(A)), or administered to outpatients (even if they are self-administered) for diagnostic purposes (42 CFR 410.28). Therapeutic injectable that are routinely self-administered, such as insulin, are therefore excluded from Medicare

coverage. Whether a drug is self-administrable depends on the usual method of administration of the drug or biologic furnished by the physician. For example, oral dosage forms administered by a physician are not covered (35).

In addition, through legislation, Congress has covered specific pharmaceuticals under Part B, including certain prescription drugs provided incidental to a dialysis treatment, certain immunosuppressive drugs used in transplant therapy for one year following a Medicare-covered organ transplant, pneumococcal vaccine, and hepatitis B vaccine for certain high-risk groups.

Under Part B, pharmaceuticals furnished by physicians, community pharmacies, and independent dialysis facilities are paid on a reasonable charge basis, while those furnished by outpatient hospital facilities are paid on a reasonable cost basis. Medicare pays 80 percent of the reasonable cost of pharmaceuticals provided to patients of an outpatient hospital facility. The reasonable cost of any service is the cost actually incurred by the facility to acquire the product or provide the service, excluding any costs unnecessary for the efficient delivery of needed health services (42 USC 1395v).

Medicare pays 80 percent of the reasonable or approved charge for pharmaceuticals, after a patient has met an annual deductible, currently $75. The patient pays the remaining 20 percent, plus any difference between the actual charge and Medicare's approved charge. HCFA regulations define the reasonable or approved charge as the portion of the charge that is approved for payment by Medicare. The amount is determined by the Medicare contractor according to guidelines developed by HCFA. The approved charge is defined as the lowest of 1) the physician's or supplier's customary charge for that service, 2) the prevailing charge for similar services in that locality, 3) the actual charge made by the physician or the supplier, or 4) the contractor's private business charge for comparable service (35). The method of deriving payment rates for the approved charge is termed the customary, prevailing, and reasonable (CPR) method. For injections, determination of the approved charge is often based on prices in the ***Redbook, Bluebook,*** or ***Medispan,*** which are compendia of pharmaceutical price information (155). The approved charge for injectable, such as recombinant erythropoietin, is based on the cost of the injectable and any supplies used to administer it plus a maximum of $2 for the accompanying staff time (155).

Patients who purchase covered Part B pharmaceuticals from non-Medicare providers, such as community pharmacies, must submit a Medicare claim to the Medicare carrier. Patients are reimbursed at 80 percent of the approved charge for the product (126).

Prescription Drug Coverage Under the ESRD Program

Through the composite rate, Medicare pays for certain routine prescription drugs commonly provided as part of a dialysis treatment. Examples of these drugs include insulin, heparin, protamine, mannitol, saline, xylocaine, antiarrythmic drugs, and antihypertensive medications (151).

Dialysis facilities may bill Medicare separately for other non-routine drugs that may be needed during a dialysis treatment, but are not included in the composite rate. Examples of these drugs include compazine, gentamycin, demerol, morphine, vancomycin, and defer examine. Payment is made for the pharmaceutical and any supplies used for its administration; no additional payment is made for staff time used to administer a pharmaceutical (151).

Hepatitis B Vaccine

The enactment of the Deficit Reduction Act of 1984 (Public Law 98-369) established Medicare coverage for hepatitis B vaccine furnished to a Medicare beneficiary at high or intermediate risk of contracting hepatitis B (150). Hepatitis B is a bloodborne infection that can result in severe morbidity and even death (27). Dialysis patients were included in the high-risk group because they frequently receive blood transfusions. Medicare also pays the facilities for staff time, supplies, and syringes involved in administration of the vaccine (150).

At the time of Medicare coverage of the vaccine, there was only one supplier in the market. In its reimbursement guidelines, HCFA cautioned its con-

tractors that, when they determined the approved charge, lack of competition in the marketplace should not result in overpayments to facilities. The contractor was to consider trade or quantity discounts on purchases of the vaccine that were available to medical providers. In addition, Medicare pays only for the quantity of vaccine that is actually administered to the patient (150). For example, if a facility purchased a vial of hepatitis vaccine for $100 and administered two-thirds of the vial, the reimbursement based on the approved charge method would be approximately $67.

Immunosuppressive Drugs

The enactment of the Omnibus Budget Reconciliation Act of 1986 (Public Law 99-509) established Medicare coverage for certain immunosuppressive drugs for one year after a Medicare beneficiary's discharge from an inpatient hospital stay during which a Medicare-covered organ transplant was performed. The change in the law was precipitated by FDA-approval in 1983 of the immunosuppressive drug cyclosporine, whose annual treatment costs were estimated to be about $5,000 per patient (126). In addition to cyclosporine, the act extended coverage to azathioprine, antithymocyte/globulin, and muromonab-CD3 (153). In December 1987, Medicare coverage was expanded to those drugs that are not used exclusively as immunosuppressive drugs, but that are commonly used as part of immunosuppressive therapy, such as the steroid prednisone.

MEDICARE'S CURRENT COVERAGE AND PAYMENT POLICIES FOR RECOMBINANT erythropoietin

In developing payment rates for recombinant erythropoietin, HCFA had to consider the various facilities in which it would be used, including hospitals, dialysis facilities, physicians' offices, HMOs, and other CMPs.

Payment rates for recombinant erythropoietin were not established for inpatient facilities or CMPs. Medicare pays for recombinant erythropoietin administered to inpatients through the DRG rate. Any additional cost to the facility of using recombinant erythropoietin, however, will not be reflected in a DRG until the rates are recalculated in the future. Similarly, Medicare pays CMPs for use of recombinant erythropoietin through the monthly cavitation payment (126).

Dialysis Facilities

Initial Payment Policy

In July 1989, HCFA issued special coverage and payment instructions to its intermediaries for administration of recombinant erythropoietin to patients in hospital-based and independent dialysis facilities. Coverage was retroactive to June 1, 1989, the day FDA approved recombinant erythropoietin for anemia associated with chronic renal failure. (154).

HCFA determined that it would pay both hospital-based and independent dialysis facilities $40 for any recombinant erythropoietin dose of 10,000 units or fewer, and an additional $30 for any dose over that amount,[6] (154). Payment was to be made in addition to the composite rate and restricted to administration in a dialysis facility. No additional payment would be made for the staff time or supplies involved in administering recombinant erythropoietin. HCFA assumed that the composite rate adequately covered these expenses, and no increase was made in the composite rate. A review of HCFA payment policy for recombinant erythropoietin administered in dialysis facilities commenced in December 1989 (126).

If a dialysis patient received 10,000 units of recombinant erythropoietin or fewer at each of 3 weekly dialysis sessions, for a total of 156 sessions per year, the annual per patient cost would total approximately $6,240. Medicare would pay 80 percent of the costs ($32 per administration), or $4,992, and the patient would pay the remaining 20 percent ($8 per administration), or $1,248 per year in cost-sharing, if one assumes that the patient had previously met the $75 annual Part B deductible.

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6 For doses over 10,000 units, HCFA requires that additional information be reported to the intermediary or carrier, including incidence of iron deficiency, Vitamin B12 or folic acid deficiency, hemolysis, or unrecognized blood loss (1S4).

Self-Administration of Recombinant erythropoietin

Since the Social Security Act prohibits Medicare from paying for self-administration of pharmaceuticals (42 CFR 410.29a), Medicare may not pay for dialysis or other patients to self-administer recombinant erythropoietin. This prohibition affects the approximately 18,000 patients that perform dialysis at home (156). Under current regulations, dialysis patients may self-administer certain drugs in the home setting that are considered dialysis supplies, such as heparin; local anesthetics, such as xylocaine; and antibiotics for peritoneal dialysis patients, when used to treat infections of the catheter site (151).

Method Used To Establish Initial Payment Rates

HCFA established an initial recombinant erythropoietin outpatient payment rate shortly after the agent was approved (see app. E). Approximately 1 year prior to the anticipated approval of recombinant erythropoietin, Amgen and HCFA entered into discussions about payment rates (25). HCFA recognized that recombinant erythropoietin would represent a significant expense for the Medicare ESRD program and for dialysis patients and that HCFA should have an appropriate payment policy ready for its intermediaries. Amgen recognized that the Federal Government, through the Medicare ESRD program, would be the primary payer for recombinant erythropoietin for the foreseeable future and that the payment rate set by HCFA would have a significant impact on the revenues of the company, at least for the near term.

HCFA's initial payment rate of $40 for a dose of recombinant erythropoietin at or under 10,000 units was based, in part, on an analysis of Amgen's cost of producing the amount of recombinant erythropoietin projected to be used by the dialysis population in the first year after FDA approval. HCFA was assisted in analyzing these costs by the Department of Health and Human (DHHS) Services' Office of the Inspector General (OIG) (see app. E). HCFA used this cost analysis along with other factors in setting Medicare's initial payment rate for dialysis facilities.

Several critical decisions had to be made by HCFA and the OIG in analyzing Epogen's costs of production, including estimating the market penetration of Epogen, selecting an appropriate rate of return on Amgen's investment, and identifying the percent of costs from each category that would be allocated to Epogen vs. Amgen's other products.

Based on data supplied by Amgen, HCFA estimated that 20,000-25,000 patients, or about one-fourth of the U.S. dialysis population, would receive recombinant erythropoietin in the first year after FDA approval. After estimating the total costs of production for Epogen, the OIG used this level of initial market penetration to estimate an annual per patient cost of treatment. It then divided this by the number of annual dialysis sessions to estimate a per-administration cost for Epogen.

The OIG used 20 percent as an appropriate return on investment on the grounds that the pharmaceutical industry averaged this profit rate before taxes. In addition, for each cost category, the OIG included only the portion that pertained to Epogen, not to Amgen's other products. For example, in the current research and development and the sales, general, and administrative categories, only that part of costs that the OIG estimated pertained to Epogen was included in the estimate (129).

According to a November 1989-March 1990 survey of dialysis facilities by the OIG, the selling price from wholesalers averaged $41 for the 4,000 unit vial (85). In March 1990, Amgen reported that its list price to wholesalers was $10 for 1,000 units (117). Prices of recombinant erythropoietin in the United States as of December 1989 are compared with prices in other European countries in table **4-3.** As the table indicates, the prices of the product are higher in some countries and lower in others compared with the United States.

Physicians' Offices

In November 1989, HCFA extended coverage to and issued reimbursement instructions for recombinant erythropoietin administration for dialysis patients in physicians' offices. The instructions also

Table 4-3-Prices of a 4,000-Unit Vial to Providers of Recombinant Erythropoietin, by Country, December 1989

Country	Price in country's currency	Purchasing power parities[a]	Price in U.S. dollars
Austria	694.45	16.80	41.34
Belgium	2,022.83	44.50	45.46
Denmark	3%.00	10.20	38.82
Finland	224.39	6.21	36.13
France	330.00	7.43	44.41
Germany	98.00	2.47	39.67
Greece	13,000.00	100.00	130.00
Italy	73,777.00	1,399.00	52.75
Luxembourg	2,023.00	41.00	49.34
Netherlands	114.00	2.40	47.50
Norway	383.00	8.64	44.33
Portugal	9508.00	84.10	113.06
Spain	7,200.00	106.00	67.92
Sweden	360.00	8.69	41.43
Switzerland	88.00	2.43	36.21
United States	41.00[b]	—	41.00
United Kingdom	36.00	0.58	62.00

[a] Represents the purchasing power parities (PPP) for the individual countries, a conversion factor that is based on the purchasing power of foreign currencies relative to U.S. dollars as measured for a given market basket of goods. The measures are 1987 estimates based on extrapolations from 1985 data. The source of the data is the Organization for Economic Cooperation and Development: Health Data File, 1989. Since the purchasing power of U.S. dollars relative to other currencies may have changed over the past 5 years, these measures are subject to some inaccuracy. Purchasing power parities, however, even if dated, are superior to current exchange rates, because the latter are more reflective of the relative demands for the limited goods traded among countries rather than the relative purchasing powers of the respective currencies.

[b] Based on a November 1989-March 1990 survey by the HHS Office of the Inspector General, $41 is the average price of the product to dialysis facility providers, including any markup added by the wholesaler (185).

SOURCES: Schieber and Poullier, 1989 (125); Zahn, 1989 (174).

extended coverage of and payment for recombinant erythropoietin to patients with chronic renal failure who do not yet require dialysis (predialysis patients) (155). Coverage in physicians' offices is possible because Medicare covers pharmaceuticals that are furnished incidental to a physician's professional service (Social Security Act 1861(s)(2)(A)). With the implementation of this coverage, home dialysis patients could receive recombinant erythropoietin from a local physician.

Unlike the case for dialysis facilities, for which the payment rate is $40 for up to 10,000 units of recombinant erythropoietin, Medicare pays the physician an approved charge on a fee-for-service basis; Medicare payment increases with the number of units administered to the patient and the physician's billed charge.

Medicare makes no additional payment for physician's staff time involved in administering injectable to dialysis patients. HCFA assumes that the monthly cavitation rate for physician services adequately covers this time (42 CFR 405.542). Therefore, physicians may not bill Medicare separately for time involved in administering recombinant erythropoietin to dialysis patients in their offices. The capitated physician may bill Medicare for any additional supplies, such as needles and syringes, used to administer the product (155). If a physician other than the capitated one administers recombinant erythropoietin, the administering physician may bill the capitated one for staff time. Medicare pays the administering physician only for the amount of product used and any supplies used for administration. For recombinant erythropoietin administered to non-dialysis patients, physicians may make

an additional charge for staff time and supplies used in administering recombinant erythropoietin.

MEDICAID COVERAGE OF RECOMBINANT erythropoietin

Besides Medicare, other sources of dialysis-related medical service payments are private insurance, Medicaid, and other State programs. Little information is available on the extent to which these sources cover the costs of these services, including recombinant erythropoietin and its administration.

Some information is available, however, on Medicaid coverage. Medicaid is a federally-aided, state-administered program that provides medical assistance to certain low-income people (147). Although over 90 percent of all ESRD patients' medical services is paid for by Medicare, Medicaid covers ESRD services for some individuals ineligible for Medicare, those services not covered by Medicare that a State may choose to provide under Medicaid, and cost-sharing incurred by ESRD patients who are dually eligible for both Medicare and Medicaid. Dually eligible people consist of aged, blind, or disabled Medicare beneficiaries whose income and assets are low enough to meet either Federal or State criteria for Medicaid. Approximately 3.5 million or 12 percent of the aged population fit into this category. Total State Medicaid ESRD expenditures in 1988 were estimated to be $68 million dollars, approximately half of which were paid by the Federal Government. The services covered for ESRD patients vary by State. A recent survey of Medicaid programs indicated that only 6 of 48 States cover prescription drugs as part of ESRD services (75).

As of March 1990, however, 43 State Medicaid programs paid the $8 per dose recombinant erythropoietin Medicare patient cost-sharing for eligible individuals (117). A decision had been made by five States not to pay this cost-sharing, and four States and the District of Columbia had not made a decision. Many of the States had adopted the HCFA payment policy of $40 for any recombinant erythropoietin dose under 10,000 units with an additional $30 add-on for doses over that quantity. That so many of the Medicaid programs adopted HCFA's payment rate for recombinant erythropoietin underscores the importance of HCFA's payment rates.

ESRD patients may also be able to seek financial relief for medical care costs from individual State kidney programs, some of which were operating before Medicare assumed most of the costs of ESRD treatment in 1973. These programs are generally the payer of the last resort, after all forms of public and private insurance have been exhausted. A total of 19 States operate a kidney program to provide financial assistance for ESRD patients who are not eligible for Medicaid (75). As is the case with the State Medicaid programs, the services covered by the kidney programs differ by State. Sixteen of these programs cover prescription drugs, but the extent to which these programs help defray the cost of recombinant erythropoietin is currently unknown.

Appendix A
Method of the Study

The Office of Technology Assessment (OTA) originally undertook this study of Medicare payment for recombinant erythropoietin as part of a larger assessment of Medicare payment for prescription drugs. In connection with the Medicare Catastrophic Coverage Act of 1988 (Public Law 100-360), the House Committees on Energy and Commerce and on Ways and Means and the Senate Committee on Finance jointly requested OTA to examine alternative payment policies for the prescription drug benefit added by the Act. The Senate Special Committee on Aging also requested the study. In April 1989, OTA's Technology Assessment Board (TAB) approved an OTA study on prescription drug payment to start in July 1989. In the context of the larger study, in May 1989 the House Committee on Ways and Means, Subcommittee on Health also asked OTA to study payment strategies that Medicare might apply to recombinant erythropoietin, which was about to be approved by the Food and Drug Administration.

The advisory panel for the parent assessment, "Medicare's Prescription Drug Benefit: Alternative Payment Policies," which consisted of 22 people from pharmaceutical manufacture, distribution, and dispensing; medicine; consumer advocacy; economics; law; and insurance, initially provided guidance for the study on recombinant erythropoietin (see app. C). At its meeting in September 1989, the advisory panel reviewed background material prepared by OTA staff on policy issues related to Medicare payment of recombinant erythropoietin and suggested additional sources of information and payment policies to consider.

During the fall and winter of 1989, OTA staff met with representatives of companies manufacturing recombinant erythropoietin; staff of Federal agencies responsible for policies related to recombinant erythropoietin, chiefly the Food and Drug Administration and the Health Care Financing Administration; and health services researchers with expertise on Medicare's End-Stage Renal Disease Program. OTA staff also visited two dialysis centers, one hospital-based and one free-standing, and discussed issues of recombinant erythropoietin with their nephrologists. In addition, OTA staff reviewed the published and unpublished literature on the efficacy and safety of recombinant erythropoietin and on economic topics pertaining to payment options. The Food and Drug Administration (FDA), the Health Care Financing Administration, and the Department of Veterans Affairs provided information on their relevant regulations and guidelines.

In February 1990, OTA convened a workshop to discuss the draft report. Workshop participants included people from the following fields: manufacture of recombinant erythropoietin, wholesale distribution of pharmaceuticals, provision of dialysis services, nephrology, consumer advocacy, economics, Medicare policy, FDA policy, consumer advocacy, pharmacy administration, and law (See app. B). In addition to the workshop participants, the draft report was sent for review to members of the advisory panel for the broader study of Medicare's prescription drug benefit[1] and to others from a range of disciplines and interests. During February and March 1990, OTA staff revised the report on the basis of the discussion at the workshop and on comments and additional material from reviewers. The staff prepared a final draft, which was submitted in late March 1990 to the Technology Assessment Board for its approval.

[1] In March 1990, in light of Congress' previous repeal of the Medicare Catastrophic Coverage Act of 1988, OTA's Technology Assessment Board rescinded approval for the study "Medicare's Prescription Drug Benefit: Alternative Payment Policies."

Appendix B

Workshop Participants--
Recombinant erythropoietin: Payment Options for Medicare

On February 20, 1990, a workshop was held to discuss the draft report. OTA staff wish to thank the participants for their review and advice.

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Appendix C
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Advisory Panel members provide valuable guidance during the preparation of OTA reports. The presence of an individual on the Advisory Panel, however, does not mean that the individual agrees with or endorses the conclusions of this particular Report.

List of ACRONYMS

AAPCC --average adjusted per capita cost
AIDS --acquired immunodeficiency syndrome
ARC --AIDS-related complex
AWP --average wholesale price
AZT --zidovudine
CAPD --continuous ambulatory peritoneal dialysis
CBO --Congressional Budget Office, U.S. Congress
CCPD --continuous cycling peritoneal dialysis
CFR --code of federal regulations
CHO --Chinese hamster ovary
CMP --competitive medical plan
CPR --customary, prevailing, and reasonable
DHHS --Department of Health and Human Services
DNA --deoxyribonucleic acid
DRG --diagnosis-related group
ELA --establishment licensing application
ESRD --end-stage renal disease
FDA --Food and Drug Administration, U.S. Department of Health and Human Services
FSS --Federal Supply Schedule
GMP --good manufacturing practices
HCFA --Health Care Financing Administration, U.S. Department of Health and Human Services
HIV --human immunodeficiency virus
HMO --health maintenance organization
ITC --U.S. International Trade Commission
IV --intravenous
kg --kilogram
NANBH --non-A non-B hepatitis
NDA --new drug application
NMC --National Medical Care, Inc.
OIG --Office of the Inspector General, U.S. Department of Health and Human Services
OTA --Office of Technology Assessment, U.S. Congress
PLA --product licensing application
PRO --peer review organization
RCT --randomized clinical trial
rHuEPO --recombinant (human) erythropoietin
RNA --ribonucleic acid
SC --subcutaneous
VA --Department of Veterans Affairs

Glossary of Terms

Access: Potential and actual entry of a population into the health care delivery system.

AIDS (acquired immunodeficiency syndrome): A disease caused by the retrovirus human immunodeficiency virus (HIV) and characterized by a deficiency of the immune system. The primary defect in AIDS is an acquired, persistent, quantitative functional depression within the T4 subset of lymphocytes. This depression often leads to infections caused by micro-organisms that usually do not produce infections in individuals with normal immunity or to the development of a rare type of cancer (Kaposi's sarcoma) usually seen in elderly persons or in individuals who are severely immunocompro-mised from other causes.

Amino acid: A group of 20 molecules that bind together to form proteins. Each type of protein is made up of a specific sequence of amino acids coded for in the DNA.

Autologous donation: A blood donation that is stored and reserved for return to the donor as needed, usually in elective surgery.

Autologous transfusion: Transfusion of blood or blood components drawn from a donor and maintained for subsequent transfusion to that same donor.

Average adjusted per capita cost (AAPCC): The AAPCC is the estimated average per capita amount that would be payable if covered services for Medicare Competitive Medical Plan (CMP) members were furnished in local fee-for-service practices. The AAPCC formula consists of the product of three major components: (1) the U.S. per capita Medicare cost as projected to the current year, (2) an adjustment based on the historical relationship between national Medicare costs and Medicare per capita reimbursements in the local area that a CMP serves, and (3) an adjustment for the differences between persons who choose to enroll in a CMP and the Medicare population at large from which CMP enrollees are drawn.

Biologics: Medicinal preparations made from living organisms and their products, including serums, vaccines, antigens, antitoxins, etc.

Biotechnology: Techniques that use living organisms or substances from organisms to make or modify a product. "New" biotechnology refers to recombinant DNA techniques and other sophisticated tools relying on the ability to harness and manipulate genetic material.

Bone marrow: A highly vascular, modified connective tissue found in the long bones and certain flat bones of vertebrates that is the origin of blood cells.

Clinical trial: A scientific research activity undertaken to define prospectively the effect and value of prophylactic, diagnostic, or therapeutic agents, devices, regimens, procedures, etc., applied to human subjects.

Coinsurance: That precentage of covered medical expenses, after subtraction of any deductible, for which an insured person is responsible. Under Medicare Part B, after the annual deductible has been met, Medicare will generally pay 80 percent of approved charges for covered services and supplies; the remaining 20 percent is the coinsurance, for which the beneficiary is liable.

Common Costs: Costs that are not traceable to any one specific product.

Continuous ambulatory peritoneal dialysis (CAPD): Peritoneal dialysis is a form of dialysis in which sterile fluid is introduced into the abdominal cavity and the peritoneum acts as the semipermeable membrane that allows the molecular exchange. In CAPD, the peritoneal dialysis is performed nearly constantly in ambulatory patients who exchange the fluid every 4 to 8 hours.

Continuous cycling peritoneal dialysis (CCPD): A form of peritoneal dialysis in which a machine cycles the dialysate in and out of the peritoneal cavity automatically about every 4 hours overnight as the patient sleeps.

Cost-sharing: That portion of the payment to a provider of health care services that is the initial liability of the patient and that may include deductibles, copayments, coinsurance, and, under Medicare Part B, unassigned liability. Also, the general set of financial arrangements under which health care insurance is contingent on a purchaser's acceptance of the obligation to pay some portion of the reimbursements for those services.

Coverage (Medicare): In the Medicare program, coverage refers to the benefits available to eligible beneficiaries and can be distinguished from payment, which refers to the amount and methods of payment for covered services.

Customary, prevailing, and reasonable (CPR) method (Medicare): The method used by carriers to determine the approved charge for a particular Part B service from a particular physician or supplier based on the actual charge for the service, previous charges for the service by the physician or supplier in question, and previous charges by peer physicians or suppliers in the same locality. **Customary charge:** In the absence of unusual medical circumstances, the maximum amount that a Medicare carrier will approve for payment for a particular service provided by a particular physician practice. The carrier computes the customary charge on the basis of the actual amount that a physician practice or supplier generally charges for a specific service. Prevailing charge: In the absence of unusual medical circumstances, the maximum amount a Medicare carrier will approve for payment for a particular service provided by any physician practice within a particular peer group and locality. Generally, this amount is equal to the lowest charge in an array of customary charges that is high enough to include 75 percent of all the relevant customary charges. Approved or reasonable charge: An individual charge determination made by a Medicare carrier on a covered Part B medical service or supply. In the absence of unusual medical circumstances, it is the lowest of: (1) the physician's or suppliers's customary charge for that service; (2) the prevailing charge for similar services in the locality; (3) the actual charge made by the physician or supplier; and (4) the carrier's private business charge for a comparable service. Also called allowed charge or reasonable charge.

Dialysate: The sterile fluid used in dialysis to remove toxic substances from the blood. The chemical composition of the dialysate varies according to the types of substances being removed. According to the basic principle of osmosis, the dialysate generally contains low concentrations of the waste substances.

Dialysis: The process of separating crystalloid and colloids in solution by the differences in their rates of diffusion through a semipermeable membrane.

Efficacy The probability of benefit to individuals in a defined population from a medical technology applied for a given medical problem under ideal conditions of use.

Efficient resource allocation: The allocation of resources among alternative uses so that maximum social benefits are derived from the resources.

End-stage renal disease (ESRD): Chronic renal failure that occurs when an individual irreversibly loses a sufficient amount of kidney function so that life cannot be sustained without treatment. Hemodialysis, kidney transplant surgery, and continuous ambulatory peritoneal dialysis are forms of therapy.

Fee-for-service payment: A method of paying for medical services in which each service performed by an individual provider bears a related charge. This charge is paid by the individual patient receiving the service or by an insurer on behalf of the patient.

Fee schedule: An exhaustive list of provider services in which each entry is associated with a specific monetary amount that represents the approved payment level for a given insurance plan.

Glycoprotein: A protein with attached sugar groups.

Good manufacturing practices: Requirements regarding the manufacturing, processing, packing, storage, and other practices involving products under the jurisdiction of the Food and Drug Administration (foods and food additives, cosmetics, drugs, biologics, and medical devices).

Health maintenance organization (HMO): A health care organization that, in return for prospective per capita (cavitation) payments, acts as both insurer and provider of comprehensive but specified medical services. A defined set of physicians provide services to a voluntarily enrolled population. Prepaid group practices and individual practice associations are types of HMOs.

Hematocrit: The volume occupied by the cellular elements of blood in relation to the total volume.

Hemodialysis: A process by which blood is pumped from the patient's body into a dialyzer and then returned to the body in a continuous extracorporeal blood loop. While in the dialyzer the blood flows next to but separate from another fluid, a dialysate. The blood and the dialysate are separated from each other by a semipermeable membrane. By diffusion and osmosis, waste products and other molecules pass through the semipermeable membrane and the blood can again take on its appropriate properties.

Hepatitis: Inflammation of the liver which may be due any of several causes, including viruses.

Hormone: A chemical substance that is released into the circulatory system by a gland that has a specific regulatory effect on another organ; functions regulated include metabolism, growth, and the development of secondary sex characteristics (such as breasts, facial hair).

Medicare carriers: Fiscal agents (typically Blue Shield plans or commercial insurance firms) under contract to the Health Care Financing Administration for administration of specific Medicare tasks. These tasks include computing reasonable charges under Medicare Part B, making actual payments, determining whether claims are for covered services, denying claims for noncovered services, and denying claims for unnecessary use of services.

Medicare intermediaries: Fiscal agents (typically Blue Cross plans or commercial insurance firms) under contract to the Health Care Financing Administration for administration of specific Medicare tasks. These tasks include determining reasonable costs for covered items and services, making payments, and guarding against unnecessary use of covered services for Medicare Part A payments. Intermediaries also make payments for home health and outpatient hospital services covered under Part B.

Non-A, non-B hepatitis (NANBH): A term used to describe hepatitis (inflammation of the liver) in which both hepatitis A and hepatitis B have been excluded. Hepatitis C has been identified as the cause of a substantial portion of NANBH.

Orphan Drug Act: Public Law 97-414, which charges the U.S. Government with identifying and promoting orphan products, defined as drugs and devices for rare diseases.

Out-of-pocket costs: Deductibles and copayments incurred by beneficiaries when services are rendered.

Peritoneal dialysis: A form of dialysis that occurs

within the patient's body, rather than via an extracorporeal blood loop as in hemodialysis. A catheter is inserted into the abdomen and then dialysate is entered through the catheter into the peritoneal cavity. The fluid is allowed to remain for varying periods of time, during which dialysis occurs across the semi-permeable peritoneal membrane. Later, the dialysate is drained out through the catheter and discarded.

Phase I, II, and 111 drug trials: The sequence of studies in human beings required for new pharmaceutical approval by the Food and Drug Administration. Phase I includes studies in a small number of relatively healthy patients or normal volunteers to determine safety and pharmacologic effects. Phase 11 includes controlled clinical trials to determine appropriate doses, safety, and effectiveness in a total of about 200 patients. Phase III trials are usually randomized clinical trials.

Protein: A molecule composed of hundreds of linked amino acids in a specific sequence, which is, in turn, determined by the sequence of nucleotides in DNA in the gene coding for the particular protein. Proteins are required for the structure, function, and regulation of the various cells, tissues, and organs in the body.

Quality of care: The degree to which actions taken or not taken increase the probability of beneficial health outcomes and decrease risk and other untoward outcomes, given the existing state of medical science and art.

Randomized clinical trial (RCT): An experiment designed to test the safety and efficacy of a medical technology in which people are randomly allocated to experimental or control groups, and outcomes are compared.

Recombinant DNA (rDNA) technology Techniques involving the incorporation of DNA fragments, generated with the use of restriction enzymes, into a suitable host organism's DNA (a vector). The host is then grown in culture to produce clones with multiple copies of the incorporated DNA fragment. The clones containing this particular DNA fragment can then be selected and harvested.

Method Used by the Office of the Inspector General to Estimate the Manufacturer's Costs of Recombinant erythropoietin

The Health Care Financing Administration (HCFA) was assisted in setting the initial rate that Medicare paid for recombinant erythropoietin by the Department of Health and Human Services' (HHS) Office of the Inspector General (OIG).[1] Based on data supplied by Amgen and other sources of information, OIG staff estimated Amgen's costs of developing and producing the amount of recombinant erythropoietin expected to be used for the dialysis population in the first year after approval by the Food and Drug Administration (FDA). HCFA used this cost estimate as one of the considerations in setting the initial payment rate for recombinant erythropoietin administered in a dialysis facility. The OIG accepted some of the cost data supplied by Amgen and modified other data.

The OIG's initial cost estimates were predicated on certain assumptions concerning use of recombinant erythropoietin in the first year after FDA approval. These estimates assumed that an average dose of 5,000 units of recombinant erythropoietin would be administered to each dialysis patient 3 times a week, for a total of approximately 156 administrations per year, and that recombinant erythropoietin would be used in 20,000-25,000 dialysis patients in the first year.[2]

The categories that the OIG used to estimate Amgen's costs were current operating expenses; research and development costs; selling, general, and administrative costs; income taxes; and payment of an appropriate rate of return to investors.

Amgen's current-year operating expenses included cost of goods sold; current research and development costs; sales, general and administrative costs; and income taxes. The cost of goods sold included the cost to produce the product, such as labor and materials; royalty payments; and product liability payments. Amgen provided the per-unit budgeted cost of goods sold for recombinant erythropoietin for the first year. Since the OIG had no historical data with which to compare these estimates, the OIG accepted Amgen's figures on cost of goods sold. The ratio of the costs of goods sold to total projected revenue for Amgen was compared with that of 19 other pharmaceutical companies and was found to be lower.

The ratio from other pharmaceutical manufacturers, however, would consist of cost of goods sold for all products made by that manufacturer including, in some cases, non-pharmaceutical products. These ratios might be equal to or lower than Amgen's if the costs of goods sold and revenues from the sales of non-pharmaceutical products were removed from the ratio calculations. For the purpose of comparing the Amgen ratio with that of other pharmaceutical manufacturers, the OIG used both the Business and Investment Almanac of 1988 and Moody's Industrial Index.

Also included in cost of goods sold category was a royalty payment of a certain percent of sales that Amgen has to make to Stanford University for its development of the recombinant gene-splicing technique used to produce erythropoietin. The estimated cost of product liability insurance, based on a certain percent of recombinant erythropoietin sales, was also calculated.

Current research and development costs were defined as the costs that would be incurred by the manufacturer in 1989 to further research and develop products under development, including recombinant erythropoietin. Past research and development

1Information in this appendix was based on personal communications with staff members from the HHS Office of the Inspector General (129).

2In December 1988, there were approximately 106,000 dialysis patients in the U.S. (1S5), and some researchers have estimated that approximately 75-80 percent are anemic (52). The OIG estimated full market penetration would take some time (129).

(R&D) costs were not included in this category. To determine the portion of total R&D on all Amgen's products to include in a cost estimate, the OIG first estimated the portion of the manufacturer's projected 1989 research and development costs that would be allocated to recombinant erythropoietin, and then estimated the portion of these expenditures that would be used for further research and refinement of recombinant erythropoietin in dialysis patients.

For sales, general and administrative costs, Amgen estimated its costs of establishing a marketing and distribution process for recombinant erythropoietin. These estimates were accepted by the OIG because there were no historical data with which the OIG could make comparisons. As was the case with current research and development costs, however, the OIG estimated the percentage of these costs that would be used for recombinant erythropoietin in dialysis patients.

Approximately 20 percent was added to the total of the above cost categories for current profit and return on historical investment. Amgen's income tax payments for the period were also estimated and included.

The OIG estimated the amount of funds invested in Amgen over the past 8 years (1981-1988), an appropriate profit or rate of return on these funds for individuals who had invested, and a period of time over which the investment would be recovered. Past incurred research and development expenses were to be included in this category.

To determine the total amount of funds that had been invested in the company prior to 1989, the OIG used, as a proxy, the value of stockholders' equity. The value of stockholders' equity was derived from analysis of the Amgen's Annual Reports and 10K reports filed with the U.S. Securities and Exchange Commission. Amgen received initial start-up funding from venture capitalists and joint ventures with other pharmaceutical manufacturers, but later obtained funds from three public stock offerings. Investments made in Amgen by other manufacturers for the purpose of licensing Amgen products or securing the rights for certain recombinant erythropoietin treatment indications were not included in the estimate of stockholders' equity.

The OIG then compounded a 20-percent rate of return on the value of the stockholder's equity for the 8-year period (1981-1988) over which these funds were invested. To determine the percentage of this amount that should be included in the cost calculations for recombinant erythropoietin, the OIG estimated the percent of company revenue over the period 1992-1995 that would be attributable to recombinant erythropoietin sales in the dialysis market. The OIG staff believed that products from Amgen's current research activities would reach maximum sales penetration in the marketplace during this period.[3] This compounded amount was then divided by 8 to determine the amount that would be included in the annual cost calculations.

After totaling the costs in all the designated categories, the OIG then calculated the annual cost per patient by dividing this total amount by the estimate of patients (20,000-25,000) expected to use recombinant erythropoietin during the first year after FDA approval. This resulted in the annual per-patient cost. This amount was then divided by the estimated number of patient dialysis sessions per year (approximately 156) to arrive at a per-treatment payment rate. HCFA used this calculated amount as only one of the considerations in setting its payment rate of $40 for any dose under 10,000 units.

In the final analysis, the OIG'S estimate of the per-unit cost of Amgen's recombinant erythropoietin consisted of approximately 27 percent for cost of goods sold; 16 percent for current research and development costs; 24 percent for sales, general and administrative costs; 11 percent for income taxes; and 22 percent for return on initial investment and profit.

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3 The OIG thought that Amgen would have two mature products in the market in that period of time, recombinant erythropoietin and granulocyte colony stimulating factor.

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