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ANALYSIS & COMMENTARY

Specialty Pharmaceuticals: Policy Initiatives To Improve Assessment, Pricing, Prescription, And Use

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ABSTRACT The value of “specialty pharmaceuticals” for cancer and other complex conditions depends not merely on their molecular structures but also on the manner in which the drugs are assessed, insured, priced, prescribed, and used. This article analyzes the five principal stages through which a specialty drug must pass on its journey from the laboratory to the bedside. These include regulatory approval by the Food and Drug Administration for market access, insurance coverage, pricing and payment, physician prescription, and patient engagement. If structured appropriately, each stage improves performance and supports continued research and development. If structured inappropriately, however, each stage adds to administrative burdens, distorts clinical decision making, and weakens incentives for innovation. Cautious optimism is in order, but neither the continued development of breakthrough products nor their use according to evidence-based guidelines can be taken for granted.

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Drugs known as “specialty pharmaceuticals” treat complex and life-threatening conditions such as cancer and rheumatoid arthritis and include most injectable and biological drugs (large-molecule drugs derived from living cells). They offer great therapeutic promise but are always expensive, frequently toxic, and sometimes misused.¹ Their clinical and economic value depends not only on their molecular structures but also on the manner in which they are used. Even the most remarkable new drug needs to be prescribed for patients with the appropriate stage and severity of illness; coordinated within an evidence-based clinical pathway; prescribed by a physician practice with the capability to manage the entire course of care; and adhered to by informed patients with insurance adequate to defray the costs.

Each new specialty pharmaceutical must pass through five principal stages on its journey from the laboratory to the bedside. These include reg-

ulatory market access, insurance coverage, pricing and reimbursement, physician prescription, and patient engagement. If structured appropriately, each stage improves performance assessment, reduces access barriers, and supports continued research and development. If structured inappropriately, however, each stage adds to administrative burdens, distorts clinical decision making, and weakens incentives for innovation. This article analyzes the five stages to highlight policy and payment opportunities to enhance the value of specialty pharmaceuticals.

Regulation Of Market Access

When it comes to drugs, the Food and Drug Administration’s (FDA’s) principal mission is to protect patient safety by preventing the marketing of pharmaceuticals and other therapies whose risks are large relative to the health benefits offered. Over time the agency has adopted a secondary goal of promoting clinical innovation

and patient access to new therapies. The increasingly complex mission requires the agency to balance the need for additional evidence against demands for timely product development and review. This has been particularly important for specialty pharmaceuticals because they typically are targeted to conditions without effective treatments and also pose meaningful risks of adverse side effects. Their clinical impacts vary across patients and over time for any one patient and depend in large degree on the manner in which they are used. The FDA, therefore, has been broadening its focus from clinical trials of safety and efficacy conducted prior to market approval to postlaunch surveillance, follow-on studies, and risk mitigation.

For twenty years the FDA has sought to accelerate market access, developing initiatives that offer provisional approval of specialty pharmaceuticals based on strong Phase II clinical trial results (conducted without a control group) instead of waiting for more-definitive Phase III studies (randomized clinical trials).^{2,3} The agency has been lowering the evidence bar for severe conditions that lack effective treatments, while keeping high the bar for drugs targeting well-treated conditions. For example, initial approval of Avastin in the treatment of metastatic breast cancer, a condition with few good treatment options, was based primarily on a single randomized study. As part of the conditional approval, the FDA required additional postlaunch trials of the drug's safety and efficacy in metastatic breast cancer. The additional evidence developed as a result of these trials ultimately resulted in the withdrawal of approval for that indication by the FDA. Reduction in the evidentiary demands for initial market access has been accompanied, appropriately, by increased requirements for postlaunch clinical trials.

Specialty drugs typically pose unacceptable risks to some patients while offering important benefits to others, and the FDA has been drawn ever more strongly into product surveillance and management after market launch. Many products now obtain market access only conditional on a satisfactory Risk Evaluation and Mitigation Strategy (REMS).^{4,5} These strategies may be as simple as patient guides but may include detailed requirements for data gathering, patient selection, monitoring, and education.

An example of an FDA risk mitigation initiative can be seen in the regulatory treatment of Tysabri (natalizumab), a monoclonal antibody used in the treatment of multiple sclerosis.⁶ Tysabri was approved for market access by the FDA in November 2004 as effective in reducing the severity of neurological symptoms but short-

ly thereafter was found to be associated with rare but severe brain infections. The agency removed it from the market in February 2005, despite protests from patients who were receiving significant benefits. The manufacturer developed a risk mitigation strategy, which required that patients have their progress monitored and the data included in a registry; physicians and patients be educated concerning the drug's risks; the drug be distributed only through authorized infusion centers; and nurses follow an established protocol to check for infection risk before each infusion.^{7,8} The FDA allowed Tysabri back onto the market in July 2006, and it has since been administered to more than 100,000 patients. The drug also has been found effective in the treatment of Crohn's disease, an autoimmune condition with few treatment options, and has been studied for the treatment of various cancers. A small number of brain infections continue to appear, however, and Tysabri's REMS has been strengthened over time.

This evolution in regulatory focus has not been without challenges. Accelerated review may expose patients to unsafe and ineffective products. Many promised postlaunch studies have been delayed or never completed at all. Manufacturers lack incentives to fund studies that may not support an already approved product, and it can be difficult to recruit patients to participate in randomized trials once a product is on the market. It can be difficult politically for the FDA to withdraw market authorization for an approved drug, even in the face of new evidence of toxicity, because patient advocacy groups and pharmaceutical manufacturers can form strong constituencies for continued market access. The FDA is highly constrained in its ability to control the manner by which insurers pay for, physicians prescribe, and patients use specialty drugs. The principal responsibility for appropriate use, therefore, lies outside the FDA's domain but within those of insurers, physicians, and patients themselves.

Insurance Coverage And Medical Management

Insurers' coverage policies and medical management initiatives build on the data used to obtain FDA market authorization but go further to incorporate evidence on real-world patterns of use and, in some cases, on the economic costs of each product. When done appropriately, these initiatives enhance the value of specialty drugs by increasing the likelihood that they will be administered to appropriate patients and according to cost-effective pathways. When done poorly, however, coverage policies and medical manage-

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ment initiatives erect barriers to access for beneficial treatments and reduce the incentives for continued pharmaceutical innovation.

FDA market authorization is a necessary but not a sufficient condition for insurance coverage. Insurance entities in many other nations use health technology assessments to prioritize drugs for reimbursement, taking into account both cost and comparative effectiveness data. In the United States, however, Medicare is prohibited from taking cost explicitly into account and faces severe limits on how much it can use comparative effectiveness data.⁹ For their part, private insurers face pressures from public opinion to extend coverage to all drugs that offer any health benefit, no matter how small, regardless of the cost, no matter how large. For some important drug classes, including oncology, insurers are subject to legislated mandates that prevent them from limiting coverage for particular products even when therapeutically equivalent alternatives are available.^{10,11}

In this context, insurers seek to manage the use of specialty drugs rather than to deny coverage altogether. Utilization management includes prior authorization, which requires the physician to document that the patient has a medical condition that can be treated by the drug in question; step therapy, which requires the patient to first try cheaper alternatives before moving to an expensive specialty drug; and quantity or dose limits, which specify the maximum number or size of doses per month. For example, three-quarters of insurers' utilization management programs for rheumatoid arthritis require prior failure on nonbiologic treatments before coverage will be available for expensive specialty drugs. More than half of the programs then require prior failure on the insurer's "preferred" biopharmaceutical, for which the plan has negotiated a price discount, before approval is granted for a nondiscounted product.¹²

Utilization management can limit patients' exposure to inappropriate drugs and lower the cost of treatment by favoring lower-price products,

but it imposes administrative burdens and creates tensions among patients, physicians, and insurers. Insurers now are seeking a compromise position in coverage policy that lies between the extremes of restricting use to narrow FDA-approved indications, on the one hand, and permitting any use prescribed by any doctor, on the other. Some insurers are shifting from drug-specific utilization management to mechanisms that encourage physician adherence to clinical pathways. Pathways combine criteria for drug selection, patient education and support, incentives to use community-based settings, and coordination with palliative and hospice care.¹³ Insurers are expanding use of clinical pathways from oncology to rheumatology and immunology.

Pricing And Payment

With specialty pharmaceuticals, nothing attracts more attention than the prices charged, which are high relative to those charged for non-specialty drugs and when compared to the prices of specialty and nonspecialty drugs charged in many other nations. The media are full of stories over price gouging and its downstream consequences: underuse of beneficial therapies; personal bankruptcies; and increasing pressures on public budgets, such as Medicare.¹⁴ At the same time, continued investment in biopharmaceutical research and development requires sustained financial commitments. Sustained investment requires high drug prices because drug developers rely on the prices charged for the present generation of drugs to support the creation of their next generation of products.

The high prices for specialty drugs reflect the costs of research, manufacturing, and distribution, which must be spread over a small number of eligible patients. Whereas traditional drugs often target "blockbuster" indications affecting millions of patients, specialty drugs typically target narrow indications affecting smaller numbers. The prices charged to private insurers also reflect the regulated market context. A large proportion of drug sales are made to public and quasi-public programs that impose legislated discounts and rebates. Manufacturers then must cover a disproportionate share of their research and development overhead from the prices charged to private payers.¹⁵ For example, a 2005 analysis by the Congressional Budget Office reported that public programs using the Federal Supply Schedule receive 27 percent mandated discounts off the list price of drugs.¹⁶ State Medicaid programs are eligible for minimum mandated rebates of 23 percent, plus further rebates pegged to increases in drug prices for

private payers. Private Medicaid managed care plans were made eligible for these rebates as part of the Affordable Care Act and sometimes negotiate discounts beyond mandated levels.

The most rapidly growing price discounts for specialty drugs derive from the federal 340B program, originally designed to promote access for indigent patients treated in safety-net facilities.^{17,18} The number of eligible provider entities now includes more than 16,000 community hospitals, academic medical centers, specialized cancer hospitals, and ambulatory care clinics.^{19,20} The discounts range from 25 percent to 50 percent off a specialty drug's list price. The 340B discounts apply even to drugs prescribed to commercially insured and Medicare patients, so long as the prescribing physician is employed by a 340B facility.¹⁷ Major 340B facilities are establishing their own pharmacies or contracting with independent pharmacies, which allow the facilities to obtain the 340B price discount even on drugs dispensed in the retail setting.

The dueling social imperatives to support innovation and ensure affordability can only be reconciled through a pattern of high launch prices for breakthrough products and declining prices for follow-on brands, such as biosimilars and generic chemotherapies. The FDA could contribute to price competition by accelerating the authorization for new drugs, streamlining the approval pathway for biosimilars, and allowing effective but potentially toxic products to remain on the market subject to risk mitigation initiatives. Policy makers could contribute by lifting coverage mandates that do not take advantage of the contemporary proliferation of therapeutically equivalent drugs. Insurers could then contribute by adopting evidence-based methods of technology assessment and negotiating prices for each drug based on its comparative clinical effectiveness.

Physician Prescription And Care Management

Physicians play a central role in determining the value of specialty pharmaceuticals. They select the course of treatment for each patient, including the drugs, doses, combinations, and durations of treatment. They decide whether to terminate aggressive therapy for patients whose disease has gone into remission or, on the contrary, into a terminal phase. Physicians can structure their practices in ways that either emphasize or neglect the manner by which patients are educated, monitored, and engaged in their own care.

The manner through which physicians are paid exerts an important influence on their pro-

Physicians play a central role in determining the value of specialty pharmaceuticals.

essional behavior. In principle, physicians prescribing specialty drugs should be reimbursed and, thereby, motivated for three distinct activities. First, physicians need to be paid for the office visits and other direct services provided to patients needing assessment, drug prescription, toxicity monitoring, and treatment modification. Second, the physicians need to be reimbursed for office-infused specialty drugs, which they typically purchase from distributors and then administer to patients in the office, an infusion center, or at home. Third, physician practices need to be reimbursed for the time devoted by their nurses and other staff in educating and engaging patients in their own health care.

Unfortunately, current physician payment methods do a poor job of compensating these three functions. Office visits are reimbursed through the professional fee schedule at rates often insufficient to cover practice costs. Physicians typically cannot charge insurers for care management and monitoring services provided online, by phone, and by nonphysician staff. Physicians' most important revenues come from the administration of office-infused drugs through a process referred to as "buy and bill." The difference between the price paid by the physician to the drug distributor and the amount received by the physician from the patient's insurer has been used to cover the costs of patient care management. However, this reliance on price mark-ups encourages physicians to prescribe the most expensive drugs, for which the mark-up is greatest, and to select doses at the high end of the acceptable range.²¹ Physicians are not compensated for the time spent managing patients' use of oral and self-injected specialty drugs, which are increasingly prevalent as research refocuses on small-molecule (chemical) pharmaceuticals.²²

Insurers have sought to replace buy-and-bill reimbursement with direct drug distribution. They contract with specialty pharmacies that purchase drugs from manufacturers and distribute them to physician offices (referred to as

Physician payment incentives would be more effective than consumer cost sharing for promoting cost-effective choice.

“white bagging”) or to patients’ homes (“brown bagging”).²³ Direct distribution removes the physician from drug acquisition but can create patient confusion and administrative complexity. Medical practices need the appropriate brand, dose, and form of each drug precisely when the patient comes in for a visit. Direct distribution often does not replace buy-and-bill practice revenues with other funds. Physicians then face incentives to refer patients to hospital-based outpatient clinics, where the prices paid to manufacturers are often lower and the reimbursement rates obtained from insurers are higher than what physicians can obtain on their own.²⁴

There exist several novel methods through which physician services could be reimbursed without creating incentives for overprescription or patient referral to hospital-based clinics. UnitedHealthcare has developed a bundled payment initiative that covers care management as well as office visits while leaving office-infused specialty drugs to be reimbursed separately.²⁵ WellPoint has developed an “oncology medical home” project that covers treatment pathways, enhanced patient monitoring, and coordination with palliative care. WellPoint pays a monthly care planning and management fee, in addition to paying the usual fee schedule for office visits and reimbursing office-infused drugs at cost without mark-up.^{26,27} The Hill Physicians Medical Group in California pays oncologists monthly for office-administered drugs; physician office visits; and care management for lung, breast, and prostate cancer (Dan Ayala, Hill Physicians Medical Group, and Ann Woo, Integrated Healthcare Association, personal communication, March 2014). Peter Bach and colleagues have described how analogous forms of episode payment could work for cancer patients covered by Medicare.²⁸

Patient Engagement And Cost Sharing

Patients exert a very important influence on the value of specialty drugs through their decisions with respect to lifestyle; self-education; shared decision making with the physician; adherence to the course of care; self-monitoring; and, more generally, engagement in their own health. Family members and community organizations can help patients obtain the greatest health benefit from the treatments prescribed. Financial incentives, in the form of cost-sharing requirements in health insurance, can either support or undermine patient engagement, depending on how they are designed.

Patients’ use of specialty pharmaceuticals fits well the economic definition of an *insurable event* and thus, in principle, should incur very little cost sharing. The patient is unable to predict the incidence and severity of most of the conditions requiring these complex medications, has little discretion in choice of treatments, and faces treatment costs that are high relative to personal income. Ironically, however, specialty drugs are burdened with particularly high cost-sharing requirements.²⁹ Patients using oral or self-injected specialty drugs can be subject to coinsurance within the drug formulary, with rates ranging from 25 percent to 50 percent, although this typically is limited by an annual out-of-pocket maximum.³⁰

There is no justification for imposing high cost sharing on patients who use specialty drugs according to evidence-based clinical criteria. To the extent that there exist multiple pathways that are clinically equivalent but incur substantially different costs, consumer cost sharing could be used to encourage use of the more economical alternatives. Physician payment incentives would be more effective than consumer cost sharing for promoting cost-effective choice, because patients often do not understand many of the complex clinical issues at stake. Consumer cost sharing also could be reduced to the extent to which the patient cooperates with the care management programs offered by the insurer and physician practice.³¹

Conclusion

The research and development pipeline is full of promising specialty pharmaceuticals. This is good for patients with rare and complex conditions but is sure to increase drug expenditures and heighten concerns over inappropriate use. New initiatives in FDA regulation, insurance coverage, pricing and payment, physician practice, and consumer cost sharing are required to ensure the value of specialty drugs. Cautious opti-

mism is in order, but neither continued innovation nor use within evidence-based guidelines can be taken for granted. ■

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