

Health Policy

Impact of Economic, Regulatory, and Patent Policies on Innovation in Cancer Chemoprevention

Henry G. Grabowski and Jeffrey L. Moe

Abstract

Chemoprevention agents are an emerging new scientific area that holds out the promise of delaying or avoiding a number of common cancers. These new agents face significant scientific, regulatory, and economic barriers, however, which have limited investment in their research and development (R&D). These barriers include above-average clinical trial scales, lengthy time frames between discovery and Food and Drug Administration approval, liability risks (because they are given to healthy individuals), and a growing funding gap for early-stage candidates. The longer time frames and risks associated with chemoprevention also cause exclusivity time on core patents to be limited or subject to significant uncertainties. We conclude that chemoprevention uniquely challenges the structure of incentives embodied in the economic, regulatory, and patent policies for the biopharmaceutical industry. Many of these policy issues are illustrated by the recently Food and Drug Administration–approved preventive agents Gardasil® and raloxifene. Our recommendations to increase R&D investment in chemoprevention agents include (a) increased data exclusivity times on new biological and chemical drugs to compensate for longer gestation periods and increasing R&D costs; chemoprevention is at the far end of the distribution in this regard; (b) policies such as early-stage research grants and clinical development tax credits targeted specifically to chemoprevention agents (these are policies that have been very successful in increasing R&D investment for orphan drugs); and (c) a no-fault liability insurance program like that currently in place for children's vaccines.

The significant progress over recent years in oncology has mainly been in developing new therapeutics to treat patients with established cancers (1). Although chemoprevention agents and cancer vaccines offer great promise, research and development (R&D) investment in these therapies has been relatively limited. Preventive agents face a number of scientific, regulatory, and economic barriers that have kept R&D investment low despite the promise of important medical benefits and outcomes (2).

“Chemoprevention” entered the cancer research lexicon in 1976 through the work of Michael Sporn, M.D., (3) and has advanced into U.S. and global markets through new products such as Gardasil® [a quadrivalent human papillomavirus (types 6, 11, 16, and 18) recombinant vaccine]. Some existing agents for cancer therapy or other standard applica-

tions are adding new indications for use in cancer chemoprevention or “risk reduction” For example, tamoxifen was a standard breast cancer therapy drug before it was extensively tested in, and approved by the U.S. Food and Drug Administration (FDA) for, breast cancer risk reduction (4, 5); Evista® (raloxifene) was a standard osteoporosis prevention and treatment drug before it also was thoroughly tested and FDA approved for breast cancer risk reduction (5).

Investment in basic research and clinical trials has increased for medicines specifically developed for cancer prevention and for re-purposing existing medicines for preventive purposes. However, these new preventive therapies are difficult to bring to commercialization when subjected to existing policies designed to build an armamentarium of chronic and acute treatments and diagnostics.

This article will review and analyze how various policy actions would lessen or exacerbate the barriers to R&D investment in cancer chemoprevention. Given that underinvestment in chemopreventive agents is associated with the unrealized promise of sizeable social benefits, it is appropriate to consider policy options that would be applicable to pharmaceuticals in general and to class-specific drugs in particular. The former options would include changes in patent and market exclusivity policies; the latter could involve special R&D tax credits like those used for orphan drugs. These options are discussed below.

Authors' Affiliation: Department of Economics and the Fuqua School of Business, Duke University, Durham, North Carolina
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Requests for reprints: Henry G. Grabowski, Duke University, Box 90097, Durham, NC 27708. E-mail: grabow@econ.duke.edu.

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Barriers to R&D Investment

The pharmaceutical R&D process and chemoprevention agents

Pharmaceutical R&D is a complex, costly, risky, and time-consuming process involving numerous successive stages, usually over the course of 10 or more years, with each stage having its own unique set of risk factors. Failure can occur at each step of the process for a myriad of reasons, including, but not limited to, toxicity, carcinogenicity, manufacturing difficulties, inconvenient dosing characteristics, inadequate efficacy, and economic and competitive factors.

Drug development costs, which can involve up-front investments of several hundred million dollars, are high for a number of reasons (6). For example, the size and complexity of clinical trials have been growing significantly over time. Furthermore, there is still a high level of uncertainty in the R&D process. Drugs that do manage to make it to market vary greatly in the revenues they generate for manufacturers (7), adding to the risks of drug development.

Oncology drugs carry specialized risks and development delays that could be offset by priority and expedited review policies for treatments that satisfy unmet needs and provide promising treatments of patients with terminal illnesses. However, these shorter review times are offset by greater difficulties in recruiting patients and the extended time required to fully achieve trial end points for assessing efficacy, especially in cancer chemoprevention trials. As a result, U.S. clinical trials for oncologic agents were, on average, 1.5 years longer than trials of nononcologic agents (1). These obstacles can increase considerably when considering only cancer chemoprevention drugs.

Even after a product is approved for marketing, extensive R&D expenditures are frequently undertaken for new indications and improved formulations. Studies to establish new indications typically involve expenditures of well over \$100 million but can be substantially greater when a large number of trial subjects is required, as would be the case for chemoprevention (6). Testing the cancer chemoprevention potential of a drug approved by the FDA for another indication requires trial designs that differ substantially from and usually cost substantially more than the original trials.

The lengthy and costly R&D process for a new cancer prevention indication is exemplified by the history of Evista (raloxifene). Raloxifene received its first FDA approval, which was for osteoporosis prevention, on December 9, 1997. The trials supporting this indication produced secondary data suggesting that breast cancer risk reduction also was a possible use for the product. Published in 1999 (8), the 2-year Multiple Outcomes for Raloxifene Evaluation study (which primarily evaluated raloxifene effects on fractures in postmenopausal osteoporosis patients) showed a secondary end point reduction in breast cancers. Additional trials on breast cancer risk reduction were also positive but raised some concerns about cardiovascular safety. Then, raloxifene was compared with tamoxifen in the pivotal Study of Tamoxifen and Raloxifene involving more than 19,000 women with an elevated 5-year breast cancer risk (based on the Gail model). Study of Tamoxifen and Raloxifene showed rough equivalency between raloxifene and tamoxifen in invasive breast cancer risk reduction, and raloxifene showed a better safety profile (5). In 2007, Evista

received FDA approval for additional labeling for breast cancer risk reduction in postmenopausal women with osteoporosis and in postmenopausal women at a high risk of breast cancer. The approval was based on clinical results from trials involving ~37,000 women and spanning ~10 years.

From an economic perspective, chemoprevention agents share a number of characteristics with the development of new vaccines for infectious diseases (9). Because they would be used by a relatively healthy population with no known evidence of cancer, these agents are developed in clinical trials that tend to be longer in duration, larger in scope, and more complex to perform for regulatory approval (versus cancer therapy trials; ref. 2). These logistics increase the costs and risks of R&D investment.

Product liability

Because, as with vaccines, chemoprevention drugs would be given to healthy individuals at a significant risk (generally) for a major disease, it is instructive to consider the case of the U.S. vaccine industry. Historically, this industry has been subject to above-average liability claims and risks. This increased risk was one of the primary factors leading to the exit of many firms from the industry in the 1960s and 1970s (10). Other reasons cited for this decline in vaccine makers included the smaller expected market sales for many vaccines compared with that of other drug therapies, the higher costs of manufacturing and regulatory compliance, and the unfavorable government purchasing policies for childhood vaccines. All of these concerns resulted in the number of vaccine manufacturers decreasing from 26 in 1967 to 17 in 1980 and to 5 in 2005.

Recognizing the important barrier that liability concerns could pose for traditional pediatric vaccines, the government established the National Vaccine Injury Compensation Program (VICP), funded by an excise tax on each dose of vaccine. This no-fault insurance program mitigated some of the liability risk and helped stabilize the environment for childhood vaccines. It is not applicable, however, to vaccines for adult patients. Adults are covered for no-fault liability if the product is also indicated for children and is recommended through the Advisory Committee on Immunization Practices (which functions under Health and Human Services in the Centers for Disease Control and Prevention) for routine administration. The chemoprevention vaccine Gardasil is recommended for women as old as 26 and for girls as young as 9 and so is covered under VICP for adults and children. It is reasonable to assume, however, that most future chemoprevention agents, like other agents, will not fall under the protection of this program. Therefore, a manufacturer of an adult chemoprevention agent would weigh the liability risks against the size of the expected sales. If the expected sales volume is small, known and unforeseeable liability risks could substantially reduce the attraction to investing in a chemoprevention agent.

The cyclooxygenase-2-selective agents Celebrex® (celecoxib) and Vioxx® (rofecoxib) have been tested for chemoprevention against many cancers (29). Rofecoxib was in clinical trials for colorectal cancer chemoprevention when excessive cardiovascular risks were identified, and the manufacturer, Merck, withdrew the product from the market. The Vioxx experience suggests that some chemoprevention therapies introduce a very complex benefit/risk calculus, making it difficult to

ascertain whether the benefit of delaying or avoiding cancer (and perhaps secondary, other benefits) outweighs the risk of serious adverse effects. (Additional product-specific examples are discussed in the extended version of this article included in Supplementary data.)

Biomedical funding gap for early-stage R&D

A growing gap has emerged in recent years in biomedical funding for early-stage preclinical R&D. This gap involves technology transfer from universities because early-stage “proof of concept” studies (which provide early evidence that a molecule may feasibly be developed for a particular use) are beyond the basic research questions typically investigated by university researchers. At the same time, many venture capital and private equity firms have pulled away from funding very early-stage discovery companies and focused instead on companies with compounds in clinical trials (11). This pulling away reflects the fact that new molecular entities can take a decade or more to achieve significant milestones, which is beyond the life of most venture capital funds.

This emerging funding gap potentially affects many promising academic programs, even those with strong intellectual property assets for licensing to start-ups and pharmaceutical firms. It is a particularly relevant issue for chemoprevention agents because many are at the earliest stages of development and are expected to have lengthy development timelines. Furthermore, they will require very large-scale clinical trials to gain FDA approval. Some potential solutions to this funding gap issue in the case of chemoprevention are discussed later in “Policies Targeted Specifically to Chemoprevention.”

Intellectual Property Policies Affecting Chemoprevention and Innovation

The importance of patents in pharmaceutical R&D

Patents serve a number of functions in the complex R&D ecosystem for new medicines (12). First, they provide a reward for invention and innovation in terms of a market exclusivity period. This is especially important in an industry characterized by very risky and costly R&D that is subject to easy imitation after a product is approved by the regulatory authorities. Second, patents serve a disclosure function so that knowledge can be publicly disseminated and built upon by subsequent inventors. Beyond these traditional rationales, patents facilitate the emerging market exchange in new technologies. Economists refer to these latter roles as signaling and transactional functions. In particular, a patent is a critical asset that signals a firm's innovative capacity. It facilitates the movement of capital for new technologies in the most productive directions (13). Without patents, it is difficult to see how this market for new technologies could function in an effective manner.

Beginning with the pioneering work of William Nordhaus in 1969 (14), economists have developed conceptual models to determine the factors that affect the socially optimal exclusivity time. The basic tradeoff is between incentives for new product development and more intensive price competition after exclusivity expires. Industries where the R&D process is costly and risky need longer exclusivity periods to realize innovation benefits, compared with those industries where innovation is easier and less costly. Similarly, when the output

of innovation has important external benefits to society, as in the case of new medicine and new indications for existing medicines, this also supports a longer exclusivity period (15). Chemoprevention has demand and supply-side characteristics that are consistent with these criteria.

The Hatch-Waxman Act

In designing a patent system or set of intellectual property rights, the key policy challenge is setting the balance between the incentives for drug innovation and the imitative price competition from generics. In the United States, the 1984 Hatch-Waxman Act was passed with these dual objectives in mind. In particular, Title I established an Abbreviated New Drug Application process to facilitate generic entry and price competition after patents expire. Under the Abbreviated New Drug Application procedure, generic firms must only demonstrate that their drug is bioequivalent to the innovator's product. Title II of the Act was directed to R&D investment incentives. Because of the long clinical trial time and regulatory review period, much of the nominal patent life of 20 years is lost prior to FDA approval. Title II provided for partial restoration of some of the patent time lost during the clinical and regulatory review process.

A recent article by Grabowski and Kyle (16) has examined actual market exclusivity periods under the Hatch-Waxman Act. Market exclusivity periods are defined in their study as the period between the introduction of the new drug and the entry of the first generic. They examined market exclusivity periods for all new molecular entities that experienced first generic entry between 1995 and 2005. The average market exclusivity period for drugs with sales in excess of \$100 million was ~11 years, with a large variance around this value.

Another key finding is that generic competition has intensified over the period from 1995 to 2005. For drugs with significant market sales at the time of patent expiration, the innovator's brand typically loses more than 90% of its market within a few months' time (16). Generics now account for more than 50% of all U.S. prescriptions. Since 2001, the growth in total prescriptions for generic products has significantly exceeded that for branded products (17).

Data exclusivity

In addition to the patent restoration provisions of the Hatch-Waxman Act, there is a new chemical entity, or data exclusivity, for a period of 5 years for innovators. In particular, a generic firm cannot rely on the innovator's data on safety or efficacy through the Abbreviated New Drug Application process until 5 years have elapsed from the date of the original Abbreviated New Drug Application approval. Data exclusivity and patents are complementary forms of intellectual property for new pharmaceuticals and biologics. Innovators generally apply for patents on compounds in the preclinical or early clinical phase of the development process. In the period after a patent is granted but before a product can be marketed, innovators must generally perform a long, risky, and costly investment process to demonstrate the safety and efficacy of a product.

Data exclusivity recognizes the substantial investment that innovators have to make in the data which demonstrate safety and efficacy to gain FDA regulatory approval. It provides a floor level of exclusivity before imitation from generics that

is especially important for compounds with uncertain or limited patent protection. Ideally, data exclusivity would delay abbreviated filings and patent challenges until innovators have had an opportunity to cover their lengthy and costly R&D investment and earn a positive return on new therapeutic candidates.

Patent challenges under the Hatch-Waxman Act

The Hatch-Waxman Act also includes a market exclusivity provision for generic firms that rewards the successful challenge of the patents of an approved product. In particular, the payoff for the first generic entrant filing an Abbreviated New Drug Application and successfully challenging the patent is a 180-day exclusivity period. Even if the odds of winning are low, the payoff of successfully challenging a patent is large. There have been an increasing number of patent challenges undertaken by generic firms early in the innovator's product life cycle (18). This is contributing to a shortening in the average time that innovators have to recoup their R&D investment (16).

A patent can be challenged on the grounds of obviousness, prior art, or double patenting. A court may determine, for example, that a drug invention was "obvious," allowing the generic challenger to enter if the 5-year data exclusivity period has expired. The issue of patent type is also relevant from a policy standpoint. Process, method of use, and formulation patents have less breadth than product patents and may be more vulnerable to challenge, although each situation must be evaluated on a case-by-case basis. It is worth noting that many important drug products, such as the first AIDS therapy, AZT (zidovudine), relied on formulation or method of use patents because their product patents had already expired. This could also be the case for many chemoprevention agents.

Litigation of chemoprevention agent patents can be expected to be particularly costly due to the complex nature of the matter, processes, and the highly specialized and scarce number of experts and legal firms experienced in this emerging field (19, 20). Small firms and individuals, and in some instances universities, may be disproportionately affected by high litigation costs and therefore under-resourced to defend claims with merit (21).

Enactment of abbreviated pathway for follow-on biologics

Congress is currently considering legislation that would create an abbreviated regulatory pathway for follow-on biologics, which are sometimes referred to as "biosimilars" or "biogenerics." Most biologics are regulated through the Public Health Services Act, which does not presently contain a mechanism for an abbreviated application such as that which exists for chemical drugs under the Hatch-Waxman Act. Biologics raise scientific, legal, and regulatory issues that make the follow-on approval process different than for chemical entities (22, 23).

Data exclusivity is a particular focus of attention in legislative proposals under consideration. Legislative proposals vary significantly on the issue of data exclusivity with competing bills having provisions ranging from zero to 14 years of data exclusivity. Data exclusivity has become a very important issue to innovators. This reflects the entrepreneurial structure of R&D process in biopharmaceuticals, the long timelines to

market approvals, and the growth of patent challenges by generic firms as a core business strategy.

Early-stage development in biopharmaceuticals is concentrated in start-ups and private firms supported by venture capital firms. Venture capital firms specialize in high risk/high return ventures. Intellectual property is a key dimension of the decision to invest in life science companies that have little other tangible or intangible assets and a lengthy period of clinical trials prior to marketing approval. Patents and data exclusivity are critical to the raising of capital from venture capital firms as well as from public market offerings and partnerships.

Success in the biopharmaceutical area is ultimately predicated on the fact that when firms develop novel and useful therapies for diseases with unmet needs, they will be able to earn significant profits over a significant product life that justifies their lengthy and costly R&D investments. Whereas many projects are terminated at a loss, a few highly successful projects can yield a significant return to the overall portfolio to justify investments in these risky enterprises (24). If these profits are endangered by uncertainty about the prospect of generic entry, through patent challenges early in the product life cycle, it will lead to a shift in venture capital portfolios away from biopharmaceutical firms.

Implications for funding of chemoprevention

Intellectual property and data exclusivity issues are of particular relevance to chemoprevention. Core patents on existing agents that have shown efficacy as chemoprevention agents may have limited time remaining before expiry. It will be difficult to justify additional costly investments in R&D for established firms and even more so for small firms, individuals, and universities where patent expiry has occurred or is imminent. The uncertainty surrounding early patent challenges also may tilt the risk-return against otherwise economically viable investment programs.

If an agent has adequate patent life, seeking new chemoprevention indications may increase the attractiveness of a patent challenge. Patent owners will therefore need the resources and resolve to protect their patents. The potential for high-cost patent litigation coupled with the likelihood that many existing agents will be near exhausting or have already exhausted their patent life may create a significant barrier for additional investment in existing agents to be tested and approved as chemoprevention agents.

Lessons from the Evista case

Data at the initial osteoporosis launch of Evista suggested that this agent was effective as a breast cancer chemoprevention agent. These early cancer prevention signals were secondary effects within the target population, female osteoporosis patients with a comorbid risk or history of breast cancer. As discussed earlier, the trials to support the cancer prevention indication were lengthy, required thousands of patients, and consequently were quite costly. Lilly's patent on the composition of Evista (composition-of-matter patent) has already expired. Its current exclusivity relies primarily on a method-of-use patent for inhibiting bone loss, which expires in 2014, and this patent is under challenge by generics. The scant 7 years of use-patent protection remaining when Evista received its cancer prevention indication in 2007, coupled with

a relatively small, incremental market for breast cancer risk reduction (beyond the osteoporosis market), make it problematic that the firm will recoup its multimillion dollar investment in the additional indication. However, the indication for breast cancer risk reduction for osteoporosis patients can provide some long-term competitive strategic advantages for Lilly and its next-generation product in the osteoporosis market.

Considerations beyond investment returns may have played an important role in the development of Evista for its cancer prevention indication. Once committed to and begun, the continued study of a drug for another indication, which began in 1997 for Evista, can be difficult to reduce or cease based on purely economic grounds, even if the size and scope of the trials needed to gain FDA approval turn out to be greater than originally expected. As in the case of Evista, the early data can be highly favorable and the desirability of filling an unmet need creates its own expectations among oncologists and patients in spite of the projected uncertain return on investment. Had the data on the cancer prevention potential of Evista been weak or identified later in the patent life, it would have been difficult for the manufacturer to justify the further investment for cancer prevention, especially when considering opportunity costs and a finite pool of development funds.

There are, however, long-term strategic considerations that also could have been important in the decision to continue the trials of Evista for breast cancer prevention, particularly considerations involving the status of Evista as the only osteoporosis drug with this additional indication. Lilly has a second-generation product, arzoxifene, which is in late-stage clinical testing. With the knowledge and experience gained from raloxifene, clinical trials for arzoxifene have been designed to simultaneously show efficacy in osteoporosis prevention and treatment and in breast cancer risk reduction. If arzoxifene shows an improvement in potency and other attributes compared with raloxifene and other osteoporosis agents, it could be positioned as the treatment of choice for all these indications in postmenopausal women.

Policy Recommendations on Data Exclusivity for New Pharmaceuticals and Biologicals

Data exclusivity in the United States and Europe

The 5-year new chemical entity data exclusivity period was put into the Hatch-Waxman Act to incentivize innovators faced with few remaining years or uncertain patent exclusivity time. However, the length of this exclusivity period now needs to be reconsidered in light of industry experiences over the past two decades. Since the 1984 Act was passed, R&D costs have more than doubled in real terms (6). At the same time, generic competition has become more intense. As discussed, generic patent challenges are occurring very early in the product life cycle.

The new chemical entity data exclusivity affords branded products a floor of effective exclusivity of 5 to 7 years, depending on how long courts take to resolve patent suits. This is insufficient time for most new drugs to recoup the up-front R&D costs and earn a positive return on this investment (25). Whereas the right to challenge a patent is an integral part of the U.S. intellectual property regime, challenges should be

deterred until innovative firms have an opportunity to earn a risk-adjusted return on their R&D investments. This is an especially important issue to R&D investment in areas like chemoprevention that are at the far end of the development spectrum in terms of costs and risks.

In the European Union, both new drugs and new biological entities receiving approval by the European Agency for the Evaluation of Medicinal Products, or by individual EU countries, receive a 10-year data exclusivity period. In particular, generic firms can file an abridged market application after 8 years from the date of first EU authorization and begin the process of development and license application. However, the license may not be effective until 10 years of exclusivity from licensing has expired. This is commonly called the "eight plus two" policy (26). Moreover, there is an additional year of data exclusivity granted for entities with significant new indications that are approved within the first 8 years after their initial approval.

U.S. legislative proposals

As discussed in Section III, data exclusivity is an important issue under consideration by Congress in connection with establishing an abbreviated pathway for biological entities. Without endorsing any particular legislation currently in discussion, we believe there are ample grounds to support a data exclusivity period toward the upper end of the spectrum being considered by legislators. One consideration is the fact that a 10-year data exclusivity period, with added time for new indications, would harmonize U.S. policies with Europe. A second point is that a recent analysis of economic data for new pharmaceuticals and biologicals introduced into the United States indicates that a 13- to 15-year period would work to closely align the data exclusivity with the time necessary for a representative new molecule to earn a positive return on large, up-front R&D investment now required for FDA approval (25, 27).

It is also appropriate to consider a longer exclusivity time for new drugs as well as biologicals. This would be a reasonable reform for policymakers to consider in the face of the increasing R&D costs for innovators and the explosion in patent challenges that has occurred in recent years. These challenges have led to higher litigation expenses and potential disincentives for R&D investments in new drugs and new indications for recently launched drugs. As such, a longer exclusivity period would help sustain a vigorous innovative process involving universities, start-up firms, and R&D partnerships. All parties could be given an opportunity to obtain a positive return on their up-front investments, with lessened concern over early litigation and generic entry.

In a longer discussion available online (Supplementary data), we describe various patent reform legislations pending before the 110th Congress and their implications for chemopreventive agents.

Policies Targeted Specifically to Chemoprevention

Tax credits and other push incentives

A longer market exclusivity period is an example of a "pull" strategy that rewards research outputs. Other alternatives to increase R&D investments could involve "push" strategies that would subsidize research inputs or lower R&D costs

specifically targeted to be chemoprevention agents. Push strategies like government grants and R&D subsidies can be particularly effective in addressing the funding gap barrier present in the early-stage development activities discussed above. As discussed, this funding gap can be particularly burdensome in the case of chemoprevention entities with their long time frames and above average clinical trial requirements. (Additional information on gaps in funding by the National Cancer Institute is discussed in the extended version of this article in Supplementary data.)

Lessons from the Orphan Drug Act

One successful policy measure involving push and pull mechanisms is the Orphan Drug Act of 1983. It was designed to increase R&D investment incentives for rare diseases and illnesses. These are defined as illnesses or conditions in the United States with a prevalence of less than 200,000 patients. Orphan Drug legislation was also enacted in Japan in 1993 and in the European Union in 1999, incorporating many provisions of the U.S. law.

The Act recognizes limited incentives to undertake R&D on rare diseases given the high costs of gaining FDA approval and more limited prospects of positive returns. The Orphan Drug Act contains three provisions to lower R&D costs. First, the Orphan Drug Act establishes a 50% tax credit on clinical trials for orphan drug indications. Second, it includes a modest clinical research grant program targeted to the earlier stages of development. Third, it requires FDA advice and counseling to sponsors in acceptable research protocols for orphan drug development. These R&D push provisions are combined with one pull incentive—a guaranteed 7-year market exclusivity for orphan drug indications that runs concurrently with any patent exclusivity terms.

The primary incentive of the Orphan Drug Act of a 50% tax credit is designed to moderate problems of adverse selection associated with an overly centralized decision process. The program operates in a decentralized market fashion rather than relying on a centralized funding approach where government officials pick the winners and losers. In particular, the developers of designated orphan drugs still have to put up 50% of the funds for the clinical trials.

There is evidence that the Orphan Drug Act has been very successful in increasing the number of new drug approvals for rare illnesses. In particular, the FDA states that “more than 200 drugs and biological products for rare diseases have been brought to market since 1983. In contrast, the decade prior to 1983 saw fewer than 10 such products come to market.” As of December 2004, the FDA had granted 1,432 orphan drug designations to pharmaceutical compounds, making the clinical trials for these orphan indications eligible for tax credits and other benefits. In addition, there have been 265 orphan drug approvals (28). Almost half of these approvals have been for new molecular entities or new biopharmaceuticals.

An analysis of data from several orphan drug approvals also indicates that a much smaller number of subjects are typically needed for FDA approval than in the case of non-orphan drugs. It is probably infeasible to approve chemoprevention agents or cancer vaccines on the basis of smaller clinical trial populations, given their likely administration to large populations after approval. However R&D tax credits, FDA counseling on acceptable protocols, and priority review of

the clinical trial data would seem appropriate options to consider for chemoprevention agents and cancer-preventing vaccines, given their relative underinvestment and substantial expected benefits.

Liability mitigation using the VICP model

The VICP is restricted to vaccines that are indicated for children. Coverage expands if the vaccine is also indicated for adults. These vaccines must also be included in recommendations for general administration by the Advisory Committee on Immunization Practices (functioning within the Centers for Disease Control and Prevention). Vaccines for chemoprevention in specific populations would not be included under the current scope of work of the Advisory Committee on Immunization Practices and therefore would not meet the current criteria for no-fault insurance. Additionally, if a chemoprevention vaccine is for adults only, it would not qualify for the VICP program under its current structure. Furthermore, many chemoprevention agents currently in clinical trials for cancer risk reduction testing are not vaccines.

A program modeled after VICP could be created, which provides no-fault coverage and reduces the liability risks associated with these products. A mechanism such as the role of Advisory Committee on Immunization Practices would also need to be created to advise which agents are eligible for coverage. An advisory group could be housed within the National Cancer Institute. Funding for liability insurance or for the administration of the program could be provided, in part, through contributions from chemoprevention agent sales as a function of prices and volumes.

Concluding Comments

Chemoprevention agents are an emerging new area of scientific promise that can lead to significant new therapies to patients at risk of developing debilitating and life-threatening cancers. However, the development of these therapies currently faces significant scientific, regulatory, and economic hurdles that have adversely affected R&D investment in these agents. It is important that policymakers address these barriers with proactive policies to stimulate new R&D investment. Our recommendations include sufficient data exclusivity for new drugs and biologicals to allow payback in high-risk, lengthy R&D investments like chemoprevention. We also recommend consideration of targeted policies that have successfully enhanced other socially beneficial areas such as the tax credits and early-stage research grants for orphan drugs and the VICP no-fault insurance approach for children's vaccines. (Additional information to support these recommendations is provided in the extended version of this article in Supplementary data.)

There are a number of promising products that are currently being investigated as chemoprevention agents (a listing of these agents can be found in the extended version of this article in Supplementary data). Many of these projects are at the earlier stages of clinical investigation. A firm contemplating annually investing tens of millions of dollars over a long time span for a new chemoprevention agent or vaccine must make these decisions on expectations about future returns. Companies will undertake these development risks for the opportunity to obtain a commercially successful product

that addresses unmet medical needs. From an economic standpoint, however, there must be expectations of significant market sales, a period of exclusivity before low-cost generic entry, and some protection against mass tort liability claims (all of which were part of the case of Gardasil). On the other hand, for medicines that target rarer types of cancers with more limited market potential, or those that are

subject to potentially rapid generic competition or entities fraught with large litigation uncertainties, development becomes very problematic. The policies recommended in this article are designed to moderate the economic barriers to innovation for chemoprevention candidates so that more of them are given the opportunity to advance through the various stages to FDA review and market approval.

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