

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

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SUMMARY

A significant percentage of all the welfare gains in the 20th century were due to the introduction of new medical knowledge and technologies. Chemoprevention agents are an emerging new scientific area that holds out the promise of delaying or avoiding a number of common cancers. But these new therapies face scientific, regulatory and economic barriers that have kept R&D investment low. This paper examines the sources of bioscience innovation—individuals, small and large firms, and universities—and the opportunities for and barriers to the development of new chemoprevention agents. Chemoprevention agents are subject to larger scale clinical trials and longer time frames between discovery and FDA approval than are other entities. As in the case of vaccine products, these agents are also subject to above average liability risks because they are given to healthy individuals. Given these characteristics, promising early stage candidates often face a funding gap in competition with other life science product candidates. The longer time frame to develop new agents and indications also means exclusivity times on core patents may be eroded or subject to significant market uncertainties.

The role and importance of patents and data exclusivity laws to innovation in the biosciences are extensively analyzed in this paper. The Hatch-Waxman Act, the expansion of the abbreviated new drug application to biologicals, data exclusivity laws, and the patent reforms before the 110th Congress are reviewed with a focus on their application to chemoprevention agents. The analysis also considers complements and alternatives to patents, “push” incentives for R&D such as tax credits, and lessons which can be learned from the Orphan Drug Act.

Based on this analysis, we conclude that chemoprevention uniquely challenges the structure of incentives embodied in the economic, regulatory, and patent policies for the biopharmaceutical industry. We offer recommendations for increasing R&D investment incentives that are applicable to the pharmaceutical industry in general and to chemoprevention in particular. In the former case, we emphasize the importance of sufficient data exclusivity times to allow payback to innovators for their R&D investments prior to generic entry through an abbreviated drug application. This addresses the long gestation periods and rising R&D costs for new biological and chemicals (with chemoprevention at the far end of the development spectrum in this regard). We also recommend that policymakers consider targeted policies for chemoprevention candidates, such as early stage research grants and clinical development tax credits. These are currently provided only for orphan drug candidates. They would address the funding gap and above average development risks associated with chemoprevention agents.

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ii. Background and Purpose

As Roy Levy and Abraham Wickelgren of the Federal Trade Commission observed in a 2001 article, “It is hard to think of many industries that have contributed as much to human welfare as the pharmaceutical industry.” (Levy and Abraham, 2001) There is indeed accumulating empirical evidence that new drug introductions have played a central role in increased longevity, enhanced quality of life, and improved labor force productivity. (Lichtenberg, 2001; Cutler and McClellan, 2001) Furthermore, recent studies have attributed up to half of all welfare gains worldwide during the 20th century to the introduction of new medical knowledge and technologies. (Nordhaus, 2003; Becker, Philipson, and Soares, 2005)

While significant progress has been made in recent years in the oncology area, the focus has been on developing new therapeutics to treat patients with established cancers. (DiMasi and Grabowski, 2007a) Although chemoprevention agents and cancer vaccines offer great promise, 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. (Herberman et al, 2006)

“Chemo-prevention” entered the cancer research lexicon in 1976 through the work of Michael Sporn, MD (Tsao, Kim, and Hong, 2004) and has advanced into U.S. and global markets through new products such as Gardasil®, Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine. Existing cancer agents such as tamoxifen and NSAIDs (non-steroidal anti-inflammatory drugs) are emerging, repurposed, for use in cancer prevention, now termed chemoprevention. Chemoprevention is the “prevention of cancer or treatment of identifiable pre-cancers.” (Kelloff et al, 2006) The treatment agents include “drugs and

vaccines, including agents or natural substances that inhibit signal transduction pathways, block the activity of oncogenes, control inflammation, thwart oxidation, and prevent cancer causing viral or bacterial infection.” (Herberman et al, 2006). The human genome project, the cascade of molecular-based research focusing on signaling and metabolic pathways, and new imaging technologies have increased the knowledge, capabilities and promise for chemoprevention many fold. (Kelloff et al, 2006)

Over the past 30 years, a number of molecular targets have been identified that are associated with many of the most common cancers (see Appendix 1). While the targets and agents, e.g. p53 or CP31398, are incomprehensible to the non-scientist; colon, breast, lung, and prostate cancers are all too familiar and among the top ten cancers in the United States leading to death and disability. (ACS 2007)

Tamoxifen is an example of a therapeutic agent used in near-term, “acute” treatment as well as longer term, or chemopreventative, risk-reduction therapy. A recently reported trial, a follow-on of an earlier work published in 2005, demonstrated a prophylactic effect, as women identified as predisposed to breast cancer showed statistically significant reductions in new breast cancers due to tamoxifen therapy. (Cuzick et al, 2007) The same study also demonstrated that side effects (deep-vein thrombosis and pulmonary embolism) associated with the drug treatment were increased in the active treatment arm of the study, and significant reductions in such side effects occurred once active treatment ended. Powles (2007) updated the “Royal Marsden” tamoxifen trial after many years post-acute treatment (average 13 years) and showed the drug, used as a chemoprevention agent, demonstrated a statistically significant reduction in “ER-positive disease”. Another finding, while based on modeling versus an actual clinical trial,

showed less optimistic results using tamoxifen as a chemoprevention agent. (Maucort-Boulch and Roy, 2006)

While these results concerning tamoxifen for chemoprevention are encouraging, much additional study with larger populations will be required to fully measure the benefits and risks. From large trials will come guidelines to identify patient sub-populations, and will most likely use “biomarkers” to track molecular-level changes associated with pre-cancerous transformations and disease progression and to identify specific and related targets for the drug intervention. (Frank and Hargreaves, 2003) The progression of this risky and costly scientific activity, which ideally would be repeated for many cancers and their various sub-types, assumes funding for the basic research and development of chemoprevention therapies is available and attractive as compared to other life sciences investment options. However, there are existing and potential economic and related legal barriers to chemoprevention research.

Cancer detection and treatment are among the costliest medical interventions and present difficult challenges to patients and providers in terms of quality of life, costs, and threat to mortality. Chemoprevention holds out the promise of delaying or avoiding cancers. Investment in basic research and in clinical trials has increased for medicines specifically developed for cancer prevention or the re-purposing of existing medicines for preventive purposes. But these new preventive or “risk reduction” therapies are difficult to bring to commercialization when existing policies are applied which were designed to build an armamentarium of chronic and acute treatments and diagnostics.

Economic, scientific and regulatory policies, in combination, form the substrate incentive structure which promotes or inhibits innovation in the biosciences and in chemoprevention specifically. As the 110th Congress considers a variety of patent, regulatory, and policy reforms,

it should do so with a specific awareness of the impact of existing policies and proposed changes upon innovation in chemoprevention. The main objective of this paper is to review and analyze how various policy actions would address or exacerbate the barriers to R&D investment in chemoprevention. The next two sections discuss the key characteristics of the R&D process with this perspective in mind. The remaining sections consider current and proposed policy actions from the standpoint of enhancing the incentives for innovation in chemoprevention.

I. PHARMACEUTICAL RESEARCH AND DEVELOPMENT (R&D)

A. The Pharmaceutical R&D Process

Pharmaceutical R&D is a complex, costly, risky, and time-consuming process. The process involves numerous successive stages, usually over the course of ten or more years, with each stage having its own unique set of risk factors. Failure can occur at each step of the process, and for a myriad of reasons, including toxicity, carcinogenicity, manufacturing difficulties, inconvenient dosing characteristics, inadequate efficacy, economic and competitive factors, and various other problems.

The FDA (2002) estimates that “[n]o more than 5 in 5,000 tested compounds pass... preclinical trials and are proposed for clinical studies.” While the success rates of drugs in clinical testing are greater than in the preclinical setting, the failure risk is still substantial. DiMasi, Hansen and Grabowski (2003) analyzed the success rates of new chemical entities that began testing in humans in the 1980s and 1990s. The estimated probability of a drug entering Phase I receiving marketing approval was slightly above 20 percent in that study. A recent FDA White Paper (FDA, 2004) found less encouraging success rates, where a compound in Phase I was “estimated to have only an 8 percent chance of market success.” Therefore, more than 80%

of all drugs that enter clinical testing ultimately fail to receive marketing approval in the United States.

Drug development costs can involve up-front investments of several hundred million dollars. They are high for a number of reasons. (DiMasi, Hansen, and Grabowski, 2003) 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 also vary greatly in the revenues they generate for manufacturers. (Grabowski, Vernon, and DiMasi, 2002) This also adds to the risks of drug development.

Oncology drugs carry specialized risks and development delays which could be offset by priority and expedited review policies for treatments that satisfy unmet needs and provide promising treatments of patients with terminal illnesses. Cancer treatments and prevention agents more frequently qualify for and receive priority review at the FDA, achieving shorter review times, and have more frequently received expedited review due to promising results for terminally ill patients. But these shorter review times were offset by greater difficulties in recruiting patients and the time required to fully achieve treatment endpoints to assess efficacy. As a result U.S. clinical trials for oncological agents were on average 1.5 years longer. (DiMasi and Grabowski, 2007a)

The lengthy R&D process and its associated uncertainties are exemplified in the history of Avastin® (bevacizumab), the first of a new class of drugs to treat colorectal cancer. Almost two decades ago in 1989, Dr. Napoleone Ferrara, a scientist working for Genentech, made a discovery that would ultimately lead to the development of the first anti-angiogenesis treatment for cancer. Angiogenesis refers to the formation of new blood vessels, and anti-angiogenesis is a targeted therapy to prevent tumors from creating new blood vessels in order to stop tumor

growth. The critical finding by Dr. Ferrara was the existence of a specific angiogenic growth factor known as vascular endothelial growth factor (VEGF) which is secreted by some cancer cells. VEGF was found to attach to a protein and then signal the cell's control centers to begin growth and formation of new blood vessels. Four years later in 1993, Dr. Ferrara and his team published a key study demonstrating that an anti-VEGF antibody can suppress angiogenesis and tumor growth in preclinical models. It was not until 1996, however, that Genentech scientists were able to "humanize" an anti-VEGF antibody. As a result, Genentech submitted an investigational new drug application for bevacizumab to the FDA in 1997. The clinical trials process and regulatory review of the data took another seven years. Finally, in February 2004, 15 years after Dr. Ferrara discovered the existence of VEGF, the FDA approved Avastin® as the first angiogenesis treatment for cancer. (Flanagan, 2006)

Even after a product is approved for marketing, extensive R&D expenditures are frequently undertaken for new indications and improved formulations. This is also illustrated by bevacizumab. At the current time, bevacizumab has more than 300 clinical trials in progress for different types and stages of cancer. The compound has attracted interest for chemoprevention, although no clinical trials for this indication have commenced. Estimates of study costs for in-market drugs seeking new indications vary by the number of subjects and how the study is designed and statistically powered. The studies for the purpose of establishing new indications typically involve expenditures of well over \$100 million for the representative new drug introduction but can be substantially greater when a large number of trial subjects are required, as would be the case for chemoprevention. (DiMasi, Hansen and Grabowski, 2003)

Chemoprevention, as a clinical endpoint, can require trial designs to be significantly re-designed with concomitant increases in costs. [NOTE: A future white paper, scheduled for release in late

2007/early 2008 and also sponsored by C-Change, will discuss chemoprevention clinical trials design.]

From an economic perspective, chemoprevention agents share a number of characteristics with the development of new vaccines for infectious diseases. (Grabowski, 2005a) Because they would be utilized by a healthy population, clinical trials tend to be longer in duration, larger in scope, and more complex to perform for regulatory approval. (Herberman et al, 2006) This increases the costs and risks to R&D investment. By “healthy population” we mean patients with currently undetected cancers who have shown a pre-disposition for cancer resulting from bio-marker analysis, a previous cancer or by family history. Given the unrealized promise of sizeable social benefits associated with the underinvestment in these agents, it is appropriate to consider policy options generally applicable to all pharmaceuticals as well as class-specific ones. The former would include changes in patent and market exclusivity policies, while the latter could involve special R&D tax credits like those utilized for orphan drugs. These are discussed below.

B. Product Liability

Given that oncology drugs are targeted to life-threatening diseases, there is a general willingness on the part of regulators, physicians, and patients to accept a greater risk for therapies with significant expected benefits. As a consequence, there are many examples of oncology drugs that have been given priority review by the FDA but also carry black box warnings at the time of initial approval. The Federal Register describes the black box warning as “special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed in a prominently displayed box. The boxed

warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.” (Food and Drugs, 2001)

A relevant example is the drug Herceptin. This drug was approved by the FDA in 1998 with a review time of slightly less than five months. Herceptin constitutes an important advance in the treatment of breast cancer patients that express excessive HER-2 protein. However, treatment with Herceptin also significantly increases the risk of congestive heart failure. (Herbst et al, 2006) Consequently, the drug was given both priority review as well as a black box warning at the time of initial approval.

The COX-2 class agents, Celebrex® (celecoxib) and Vioxx® (rofecoxib) have been tested for chemoprevention against many cancers. (NCI, 2007) Rofecoxib was in clinical trials for colon cancer chemoprevention when excessive cardiovascular risks were identified and the manufacturer, Merck, withdrew the product from the market. Sponsored by the National Cancer Institute, celecoxib continues to be in clinical development for chemoprevention in cancers of the head and neck, rectum, breast, lung, bladder, ovary, and skin. (NCI, 2007) Herceptin and Vioxx experience suggest some chemoprevention therapies introduce a more complex benefit/risk calculus where delaying or avoiding cancers comes with increased side effect risks.

Given that chemoprevention drugs would be given to healthy individuals who are at significant risk for cancer, it is instructive to consider the case of the U.S. vaccine industry. Historically, the industry has been subject to above-average liability claims and risks. This increased risk was one of the primary factors that caused many firms to exit the industry in the 1960s and 1970s. (Grabowski and Vernon, 1997) Other reasons cited for this decline included the smaller expected market sales for many vaccines compared to other drug therapies, the higher costs of manufacturing and regulatory compliance, and the unfavorable government

purchasing policies for childhood vaccines. As a consequence of liability concerns and these other factors, the number of vaccine manufacturers decreased 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 adolescent or adult patients (for example, the adult vaccinations for hepatitis A or B or those for adolescent girls and adults for the human papilloma virus). Therefore, with adult vaccines being excluded from this no-fault program, it is reasonable to assume that chemoprevention agents, likewise, will not fall under the protection of this program.

Moreover, while liability concerns do not preclude successful product introductions for preventive medicines, they add to the barriers which those products face. The vaccine for Lyme disease provides an example of the potentially adverse consequences associated with administering a new product to a healthy population. The vaccine was launched in 1998 and initial sales were encouraging. However several liability suits emerged which alleged that the product caused chronic arthritis. While two large epidemiological studies found no support for these claims, sales declined significantly as a result of the large media scrutiny and attention. GlaxoSmithKline expended significant effort to defend the product, but eventually withdrew it from the market in 2002. (Berndt, Denoncourt, and Warnert, 2007)

C. The Importance of Patents in Pharmaceutical R&D

Patents are a critical feature of pharmaceutical innovation. The reason for this follows directly from the characteristics of the process of pharmaceutical innovation. As discussed, it typically takes hundreds of millions of dollars to discover, develop, and gain regulatory approval for a new drug. (DiMasi, Hansen, and Grabowski, 2003) By contrast, imitation costs are extremely low relative to the innovator's cost to discover and develop a new compound. Under provisions of the Hatch-Waxman Act, the cost of a generic to show bioequivalence and gain FDA approval has been estimated to be about \$1 million and take one to two years. (Reiffen and Ward, 2005) Therefore, absent patent protection or some equivalent barrier, imitators could free-ride on the innovator's FDA approval and duplicate the drug for a small fraction of the originator's cost.

Economic studies demonstrate the importance of patent protection to pharmaceutical innovation. For example, several studies have found that the pharmaceutical industry places the highest importance on strong patent protection to support research and development activities. (Levin et al, 1987; Cohen, Nelson, and Walsh, 2000) A study by Mansfield (1986) also found that 60 percent of the innovations commercialized by pharmaceutical firms would not have been developed without patent protection. This is far greater than the average across all industry sectors of 14 percent. These findings demonstrate that other industries have market-based forces, including the cycle time for development of their intellectual property, which can act as substitutes or complements to patents. These other forces can be equal to or greater than patents in driving innovation in that industry sector. Pharmaceuticals, by contrast, have a unique reliance on patents to attract and sustain investment necessary for innovation.

One of the strengths of the U.S. system with the life sciences is its R&D “ecosystem”, stretching from basic university research through small specialized research boutiques to large multinational firms with extensive R&D infrastructures. This ecosystem is nourished by the strong public support of basic biomedical research and the favorable technology transfer policies for universities under the terms of the Bayh-Dole Act of 1983. Universities and government labs do not typically develop new drugs but can be a source of promising new concepts and research tools that are often licensed to biotechnology and pharmaceutical firms. The U.S. also leads the world in new start-ups in the life-science and information-technology sectors. Many partnerships and joint ventures now exist between the larger pharmaceutical and biotechnology firms and these new venture companies.

Patents serve a number of functions in this complex R&D ecosystem. (DiMasi and Grabowski, 2007b) First, they provide a reward for invention and innovation. 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. (Pammolli and Rossi, 2005) Without patents, it is difficult to see how this market for new technologies could function in an effective manner.

II. OTHER POLICIES AND PERSPECTIVES RELEVANT TO CHEMOPREVENTION AND INNOVATION

A. Individuals, Small Firms, and Universities as Sources of Innovation

A significant source of innovative new biopharmaceutical compounds are small firms or individuals. (Schacht, 1999; National Academy of Engineering, 1995). Government and university research studies have suggested that small firms are more willing to take substantial risks on new technologies and possess greater agility in finding market opportunities. (Rautiainen, 2001; Baumol, Litan, and Schramm, 2007) Alternatively, large firms have established markets and can fund R&D projects from internally generated cash flows and retained earnings. As small firms and individuals lack these large firm resources and capabilities, they are highly dependent upon the patent system for their ability to raise capital and achieve commercialization of a biomedical product. (Hawkins, 1995) There is virtually no disagreement that owning a patent is a necessary condition for a small firm in the life sciences to attract the capital required to commercialize a new chemical or molecular entity.

Just as small firms and individuals play a significant role in innovative research leading to commercialized biomedical products, in the past 25 years the university has assumed a far greater role. With the passage in 1980 of the Bayh-Dole Act and later the Stephenson-Wydler Act, universities have significantly increased new rights to patent federally-funded research discoveries. (Rai and Eisenberg, 2003) Prior to 1980, universities received fewer than 250 patents annually, compared with 3000 per year by 2002. (Association of University Technology Managers, 2003) Bayh-Dole's policy goal was to increase the investment of private sector development funds for translating university research funded by federal monies into new products and processes. These private funds are essential in taking discovery research results

past the *Nature* or *Science* published article and across the remaining chasm of “commercialization” steps, which makes a biomedical breakthrough available to patients in the marketplace. Overall, this technology transfer process has created a number of societal benefits. (National Academy of Sciences, 2004) However, it has also created tensions and issues concerning the boundary of between the public commons of basic knowledge versus the appropriation of this knowledge for applied research purposes. (Mazzoleni and Nelson, 1998; Walsh, Arora and Cohen, 2003; Kesselheim and Avorn, 2007)

One important issue that has emerged in recent years regarding technology transfer is a growing biomedical funding gap associated with early stage pre-clinical R&D. These “proof of concept” type activities (studies which provide early evidence 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 (VC) and private equity firms have pulled away from funding early-stage discovery companies and focused instead on companies with compounds in clinical trials. In part, this was a response to the “genomics bubble” that occurred in the early part of this decade.

The excitement preceding and accompanying the announcement of the “working draft” of the human genome sequence in 2000 created a surge of interest and private investment in genome-based projects. But assumptions about the timeframes required to commercialize a gene-based product and the market acceptance of these new products were unrealistic, thus a period of over-investment followed by negative returns, a bubble. In particular, there was a wave of funding for “discovery target” companies, only to have VC funds belatedly realize they were so far from any business type exit events that they could not yield a profitable return within the normal life span of a VC fund. (Klausner, 2005) VC’s make high risk investments based on

assumptions regarding the time period in which their funds must remain invested. An “exit event” is the expected timing when VCs can reclaim their investment, ideally with an accompanying gain commensurate with their risk. When exit timing is delayed, the risk increases and the expected return on the initial investment can become increasingly difficult for the investor to capture.

This emerging funding gap potentially affects many promising academic programs, even those with strong intellectual property (IP) assets for licensing to start-ups and pharmaceutical firms. It is a particularly relevant issue for chemoprevention agents, given the fact that many are at the earliest stages of development and are expected to have lengthy development timelines. They will also require very large-scale clinical trials in order to gain FDA approval. Some potential solutions to this funding gap issue in the case of chemoprevention are discussed in Section V below.

The private investment funding gap has been exacerbated by an accompanying public funding gap, resulting from reductions in government-based biomedical research funding through the National Institutes of Health. In 1998 the Congress set a goal of doubling NIH funding from that year’s investment of \$13.7 billion. They succeeded a scant 5 years later when NIH funding increased to \$27.1 billion in 2003. Research institutions grew their facilities and faculties in response to this federal funding growth, expecting they could increase the number and scope of projects funded through NIH. However, since 2003, the annual increases have dropped dramatically year on year (3.1% year on year increase, 2003-2004), while the number of proposed projects has grown each year, finally to 33,000 in 2006. “ ‘What’s chilling about the [NIH] drought is that ‘we’re getting into years 3 and 4 with no end in sight,’ says Edward Benz Jr., the president and CEO of Dana-Farber Cancer Institute in Boston. Many researchers noted

that the pressures on the federal budget, including the war in Iraq, leave Congress little room to expand or even stabilize other programs.” (Science, 2007) Recently, the Association of American Cancer Institutes testified before Congress, “continuing decreases to the budgets of the NIH and NCI (in actual dollars and as a result of biomedical inflation), grants to support cancer researchers as they discover new treatments for cancer and strategies to prevent and detect the disease continue to be cut. Without these grants, fewer and fewer cancer researchers will be able to maintain their commitment to science...” (AACI, 2007) Existing, multi-year projects receive the majority of NIH funds, 77% of the 2006 budget, while the rate of acceptance for new project proposals continues to decline as the number of project applications increases. (Couzin and Miller, 2007) As such, not only has the growth in funding to the NCI decreased progressively since FY2002 (from 10.0% between 2002 and 2003 to -1.0% between 2005 and 2006), but likewise has the growth in apportionment by the NCI to chemoprevention (from 6.4% between 2002 and 2003 to -4.9% between 2005 and 2006, with a concomitant drop in percent of total NCI budget spent on cancer prevention & control from 12% in 2002 to 11% in 2006), as well as the allotment within the field of chemoprevention to new projects versus existing projects. (NCI Fact Book, 2006)

The rate of application acceptance in 2006 by all institutes within the NIH is shown below. (NIH, 2007)

Proposals Funded in 2006 By Institute

National Human Genome Research Institute 34%

National Institute of General Medical Sciences 26%

National Eye Institute 23%

National Institute of Environmental Health Sciences 22%

National Institute of Diabetes and Digestive and Kidney Diseases 21%

National Institute of Allergy and Infectious Diseases 21%

National Institute of Mental Health 20%

National Heart, Lung, and Blood Institute 20%

National Cancer Institute 19%

National Institute of Dental and Craniofacial Research 19%

National Institute of Neurological Disorders and Stroke 18%

National Institute on Aging 17%

National Institute of Child Health and Human Development 15%

(Source: NIH Extramural Research, 2006)

Since 2003 there has been a significant decline in the growth in federal funding available for biomedical research, and specifically for cancer research, thus creating a funding gap. This gap is a particular barrier to chemoprevention which is an emerging new therapy option in relative infancy.

B. Patent Protection Outside the United States

The importance of pharmaceutical patent protection can also be seen by comparing the record of pharmaceutical innovation in countries with and without strong patent protection. (Evenson and Kanwar, 2001) For example, in Japan prior to 1976, patent protection for pharmaceuticals was relatively weak in that only process patent protection was available. The Japanese system, therefore, did not encourage investment in developing new drugs. Instead, most pharmaceutical activity in Japan consisted of copying innovator drugs from abroad for sale within Japan, and there was only limited export. In 1976, however, Japan decided that it was in

its long-term interests to change these policies and amend its patent laws to allow full product patent protection for terms of 15 years. (Neary, 1995) In the three decades since making that fundamental change in its patent system, Japan has emerged as one of the leaders in pharmaceutical R&D. Over the period 1980 to 2000, for example, the number of patents related to pharmaceutical products from domestic applicants in Japan more than doubled (from 376 in 1980 to 722 in 2000), and the percentage of companies with operations in the USA and leading markets also more than doubled. (JPMA, 2007) Whereas it was formerly highly imitative, the Japanese pharmaceutical industry has become highly innovative.

On June 8, 1995, various provisions affecting patents negotiated under the GATT treaty became effective in the United States. These included changes to harmonize U.S. procedures with other countries. Most notably, the United States changed from a 17-year patent life from the date of issuance to a 20-year patent life from the date of filing. At the present time, the U.S. Congress is considering other changes to the patent system that would involve further convergence to procedures in other countries, such as a switch to a “first to file” criteria for patent awards and a new post-grant review system that would augment the current U.S. re-examination process for patents. These provisions are discussed in section IV B.

C. Data Exclusivity

Data exclusivity is an important form of IP for innovators. It is the period of time after U.S. Food and Drug Administration (FDA) approval but before a follow-on competitor can enter based on an abbreviated filing that relies in whole or part on the innovator’s data on safety and efficacy. Without a data exclusivity period, there would be little incentive to invest in developing and marketing new product candidates with few remaining years of patent protection

or with uncertain forms of protection. In addition, newly approved markets with substantial commercial sales would be exposed immediately to legal risks associated with patent challenges and early generic entry.

Data exclusivity and patents are complementary forms of IP for new pharmaceuticals and biologics. Innovators generally apply for patents on compounds in the pre-clinical 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 a product's safety and efficacy. Data exclusivity recognizes the substantial investment that innovators have to make in the data which demonstrates safety and efficacy to gain FDA regulatory approval. Ideally, data exclusivity would delay abbreviated filings and patent challenges until innovators have had an opportunity to earn a positive return on the new therapeutic candidates which successfully complete the lengthy and costly R&D process.

D. Perspectives on Optimal Exclusivity Times from Economic Analysis

Beginning with the pioneering work of William Nordhaus (1969), economists have developed conceptual models to determine the socially optimal exclusivity time. Exclusivity can originate from patents and from complementary forms of IP protection such as data exclusivity. The basic tradeoff is between incentives for new product development and more intensive price competition after exclusivity expires. In particular, longer exclusivity times encourage increased development of new drug products as well as additional research on new indications for established products. But longer periods can also postpone the onset of generic competition. When the additional benefits from expected development of more new medicines are just equal

to the additional costs of postponing the onset of generic competition, the exclusivity time is considered optimal from a social welfare perspective.

While this theoretical modeling has not yielded a specific value for the optimal exclusivity time for new drugs (or for any other industry sector), it does provide a framework to assess which industry characteristics are relevant to current policymakers' decisions in this regard. In particular, industries where the R&D process is costly and risky need longer exclusivity periods to realize innovation benefits, compared to 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. (Scherer and Ross, 1990) Chemoprevention has demand and supply-side characteristics that are consistent with these criteria.

III. LEGISLATION THAT INFLUENCES MARKET EXCLUSIVITY TIMES FOR NEW DRUGS

A. 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 (ANDA) to facilitate generic entry and price competition after patents expire. Under the ANDA procedure, generic firms must only demonstrate their drug is bioequivalent to the innovator's product. Generic manufacturers can rely on the safety and

efficacy data originally submitted by the innovator and do not have to do any clinical testing on these grounds. (Mossinghoff, 1999)

Title II of the Act was directed to R&D investment incentives. It provided for partial restoration of the patent time lost during the clinical and regulatory periods. Companies typically file their key patent application prior to the start of clinical testing. 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. The Act restores up to half the patent time lost during clinical development and the full time lost during FDA review, subject to various caps. (Mossinghoff, 1999)

In addition to the patent restoration provisions of the Hatch-Waxman Act, there is a new chemical entity (NCE), or data exclusivity, period for innovators of five years. In particular, a generic firm cannot rely on the innovator's data on safety or efficacy through the ANDA process until five years have elapsed from the date of the original ANDA's approval. This provision was included to provide some market exclusivity for drugs with little or no patent life at the time of approval.

A recent paper by Grabowski and Kyle (2007) has examined actual market exclusivity periods (MEPs) under the Hatch-Waxman Act. MEPs are defined in their study as the period between the new drug's introduction and the entry of the first generic. They examined MEPs 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 approximately 11 years. However, there is a large variance around this value. There are an increasing number of new drugs with a market exclusivity period below ten years in value. Another key finding is that generic competition has intensified over the 1995 to 2005 period.

For drugs with large market sales at the time of patent expiration (\$500 million or more) the innovator's brand typically loses more than 90 percent of its market within a few months' time.

The U.S. Congressional Budget Office (1998) has conducted an analysis of the economic effects of the Hatch-Waxman Act. With respect to R&D returns, the CBO (1998) estimated a negative effect of the Act on returns to innovators. Utilizing data from an analysis of R&D returns on pharmaceuticals combined with other information, the CBO estimated that the present value of cash flows from a representative new drug introduction declined by an average of 12 percent as a result of increased generic competition facilitated by the 1984 Act. In essence, the increasingly rapid loss of sales after generic entry has outweighed any patent term extensions provided by the Act. This can result in particularly adverse consequences for compounds of above average riskiness or those with shorter than average effective life. Chemoprevention agents and cancer prevention vaccines will frequently possess these attributes.

In the decade since the CBO study was completed, the innovative segment of the pharmaceutical industry has been characterized by a number of adverse trends. These include rising R&D costs, fewer annual new molecular entities (NMEs), declining exclusivity periods for major innovative products and more rapid erosion rates for those products after generic entry. (Cockburn, 2007; Grabowski, and Kyle, 2007) Data from the 1990s used by the CBO found that these trends have exacerbated the effects on R&D returns from the Hatch-Waxman. Indeed, a recent presentation by Doug Long, Vice President of IMS Health, noted that since 2001, the growth in total prescriptions for generic products has significantly exceeded that for branded products. (Long, 2005) These trends may intensify as several major products, such as Lipitor and Plavix, experience patent expiration over the next five years.

B. Patent Challenges Under the Hatch-Waxman Act

The Hatch-Waxman Act includes a market exclusivity provision that rewards generic firms for successfully challenging the patents of an approved product on the basis of invalidity or non-infringement. In particular, the payoff of 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. Grabowski and Kyle (2007) find that this is contributing to a shortening in the average time that innovators have to recoup their R&D investment.

Multiple law suits involving infringement have become the rule for the commercially important drugs early in the brand product's life cycle. As a percentage of ANDA filings, they have increased from 2 percent in 1984-89, to 12 percent in 1990-97, to 20 percent in 1998-2000. (Berndt et al, 2007) If a substantial fraction of these early stage patent challenges are overturned by the courts, this would likely have significant adverse effects on the long-term expectations regarding R&D returns in this industry. As of June 2002, generic firms had won the vast majority of suits, but most of these cases with outcomes to date involved late-stage patent challenges. (USFTC, 2002; Bear Stearns, 2002)

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 five-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.

From a strategic perspective, generic firms can be viewed as “prospecting” in patent suits. They are investing money in filing and litigation fees with a portfolio of patent challenges for the right to obtain a very large payoff from the 180-day exclusivity period if they win a few of these suits. However, this wave of lawsuits crowds the courts and creates uncertainty around the commercial viability of the innovator’s product. Furthermore, this uncertainty adversely affects market valuations of research-oriented pharmaceutical firms. It can cause firms to abandon R&D projects on future drug candidates with uncertain patent prospects.

Patent litigation has increased overall and particularly within the biomedical arena. (Webbink, 2005) 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. (Elleman, 1997; Thomas and Schacht, 2007) Small firms and individuals, and in some instances, universities, may be disproportionately impacted by high litigation costs and therefore under-resourced to defend claims with merit. (Lerner, 1995)

Early patent challenges with uncertain outcomes also have a chilling effect on the development of new indications and formulations. This is an important issue for cancer chemoprevention agents since many may be developed as new uses for established products several years after their initial introduction into the market. In particular, there may be no way to prevent lower cost generics from being used for the new indication after they enter the market, even if they do not have an approved label for a new indication. This is because prescriptions

are not specific to a particular indication, and pharmacists and insurers have strong economic incentives to substitute generics when they are available.

C. Enactment of Abbreviated Regulatory Pathway for Biologicals

Congress is currently considering legislation that would create an abbreviated regulatory pathway for follow-on biologicals, which are sometimes referred to as “biosimiliars”. Most biologicals 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. In considering such legislation, Congress must balance the objectives of innovation incentives and price competition, as was the case when it created a regulatory pathway for generic chemical drugs.

Biologicals present significant challenges to establishing a similar mechanism (e.g., ANDA) as abbreviated application for chemical agents. Scientific methods for establishing equivalence are so different between chemical and biological agents that “even if the biosimilar product has the same gene sequence, vector, host cell line, culture conditions and purification methods as the innovative protein, it can still differ substantially in its biological and clinical properties.” (Schellekens, 2004).

Given these challenges, the FDA will likely be given considerable discretion on clinical data requirements and will probably require some clinical trials to demonstrate comparable safety and efficacy on a case-by-case basis. The requirement of additional clinical trials will add considerably to the cost for the generic manufacturer of a biological, which would create a barrier to entry of generic competitors. Fewer competitors would decrease price competition due to generic entry after patent expiry. (Grabowski, Ridley, and Schulman, 2007)

Data exclusivity is a key focus of several rival bills that have been introduced into the 110th Congress. Current U.S. legislative proposals contain widely different provisions regarding data exclusivity. At one extreme, a bill introduced by Representative Henry Waxman would not provide for any data exclusivity for new biological entities. On the other hand, the bill recently introduced by Representatives Jay Inslee, Gene Green, and Tammy Baldwin provides for 14 years of data exclusivity. A bipartisan bill introduced into the Senate by Senators Enzi and Kennedy would provide for 12 years of data exclusivity.

D. Data Exclusivity and Biopharmaceutical Innovation

Data exclusivity assumes particular importance for biopharmaceuticals, given the fact that early-stage development is so concentrated in start-ups and private firms supported by VC. Venture capital firms specialize in high risk/high return ventures and utilize a variety of controls to assess and monitor their investments. This includes extensive due diligence and multi-stage financing with milestone targets. Risk capital is supplied in exchange for equity positions at high implicit costs of capital. Returns are realized by the VC firms when a firm in their portfolio has an initial public offering (IPO) or is acquired by a larger entity. The returns distribution for venture firms is highly skewed. While many of their 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. (Scherer and Harhoff, 2000)

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. 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 product life that justifies their lengthy and costly R&D investments and offsets many projects that fail after large investments. 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 VC portfolios away from biopharmaceutical firms. Venture capital firms are agnostic about the industries in which they invest in and can shift to information technology companies or even a new fast food chain if there is heightened uncertainty about returns from biopharmaceutical firms.

Typically, even after a biopharmaceutical firm goes public, it will need to raise additional funds to finance clinical trial activity. This generally occurs through secondary financing in the public market and/or partnerships with larger firms. In this latter regard, a rich market exchange for new technologies has emerged in the life sciences over the past two decades. A prototypical development stage agreement would involve payments for reaching particular milestones in exchange for rights by the licensee to develop and/or market the new products covered under the agreements. (Danzon, Nicholson, and Pereira, 2005; Simpson, 1998; Cockburn, 2004) IP is a critical element in the emerging markets for new technologies in life sciences and facilitates the movement of capital in the most productive directions. The prospect of extensive patent litigation with uncertain outcomes starting early in a successful product's life cycle can pose a substantial barrier to the proper functioning of these markets.

E. Implications for the Funding of Chemoprevention

Given the characteristics of the R&D process, some important implications follow for the financing of R&D investment in an innovative entrepreneurial industry like biopharmaceuticals. These are also of particular relevance to chemoprevention. First, in the early stages of

development, it is crucial to have the support of financial institutions like VC firms that can take a long-run view and a portfolio approach to such risky investments. Second, if the relatively few large successes experience increased uncertainty due to patent challenges and the potential for early generic entry, higher risk-adjusted rates of return will be demanded by VC firms, yielding fewer leads that meet this standard. Early stage R&D will be the most adversely affected segment. Such a prospect is a particularly unfavorable outcome for firms and industries whose products contribute to important long-term advancements in public health.

The development of new indications for established biological therapies would also be particularly vulnerable to early patent challenges by generic firms seeking to enter based on an abbreviated pathway. This is because obtaining approval for a new indication post-approval can take several years and involve large scale patient trials and significant costs. The uncertainty surrounding early patent challenges may tilt the risk-return against otherwise economically viable investment programs for new indications. In this case, patients would be deprived of health benefits from new indications that, in many situations, are equivalent to or surpass those of the original approved indications. (Berndt, Cockburn, and Grépin, 2006; Calfee and DuPré, 2006)

An important feature of competition for new biological entities in oncology involves new indications associated with the same or related pathways. As described earlier, at the current time, Avastin® (bevacizumab) has more than 300 clinical trials in progress for different types and stages of cancer which may include chemoprevention as an endpoint under investigation in the future. (Flanagan, 2006; Kelloff et al, 2006) This would also be an important consideration for other chemoprevention agents, since they, too, would involve the development of significant indications after initial approval.

Core patents on existing agents that have demonstrated 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. 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.

IV. POLICY RECOMMENDATIONS ON PATENTS AND DATA EXCLUSIVITY

A. Data Exclusivity for Chemoprevention Agents

As discussed, there are a number of economic factors that support a substantial data exclusivity period for new chemical and biological entities. The R&D process for these entities is long, costly, and risky. Many entities originate in start-up companies that are typically financed by venture capital firms and partnerships. This funding is very sensitive to any uncertainties surrounding the value of the firm's intellectual property assets. Furthermore, established firms are reluctant to invest in new products and new indications with uncertain payback periods. As discussed, the likelihood of patent challenges by generic firms early in the life cycle for those products that are commercially successful highlights the importance of data exclusivity periods as complements to patent protection. Chemoprevention agents, with their

higher-than-average expected clinical trial sizes, times, and other barriers, would be particular beneficiaries of a longer data exclusivity period before any patent challenge could be undertaken.

The five-year NCE data exclusivity period was put into the Hatch-Waxman Act to incentivize innovators faced with little or no 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. (DiMasi, Hansen, and Grabowski, 2003) 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 NCE data exclusivity affords branded products a floor of effective exclusivity of five to seven years, depending on how long courts take to resolve patent suits. This is insufficient time for most new drugs to recoup the upfront R&D costs and earn a positive return on this investment. (Grabowski, 2004)

In the European Union, both new drugs and new biological entities receiving approval by the European Agency for the Evaluation of Medicinal Products (EMA), or by individual EU countries, receive a ten year data exclusivity period. In particular, generic firms can file an abridged market application after eight 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 ten years of exclusivity from licensing has expired. This is commonly called the “eight plus two” policy. (Towse and Kettler, 2005) Moreover, there is an additional year of data exclusivity granted for entities with significant new indications that are approved within the first eight years after their initial approval.

As discussed, data exclusivity is an important issue in the case of an abbreviated regulatory pathway for new biological entities currently before Congress. Bipartisan legislation

in the House has provisions that would provide for 14 years, and in the Senate, for 12 years. At the same time, other legislators favor a much lower exclusivity period—either no exclusivity or the five year data exclusivity period that currently exists for new chemical entities.

A need for a significant data exclusivity period for new biologics is also supported by the economic characteristics of the R&D process. DiMasi and Grabowski (2007a) found that biologics have higher discovery and pre-clinical expenditures and longer mean clinical development times than new chemical entities. Moreover, this study found that the development of biologics involves higher development costs associated with process engineering and manufacturing than is true for chemical drugs. While biologics generally involve more complex molecules produced from large-scale cultures of living mammalian, microbial, or yeast cells, manufacturing process issues in R&D typically are more straightforward for drugs based on chemical synthesis. Likewise, the costs of constructing a new manufacturing facility or retrofitting an existing plant for such large-scale commercial production are substantially greater in the case of biologics, compared to chemical entities. (DiMasi and Grabowski, 2007a)

Without endorsing any particular legislation, we believe there are ample grounds to support a data exclusivity period at the upper end of the spectrum being considered by legislators. First, it is relevant to note that a ten year data exclusivity period would harmonize U.S. policies with Europe. At the same time, however, an analysis of economic data for new pharmaceuticals and biologicals introduced into the United States indicates that the 14-year period would more closely align the data exclusivity with the time necessary for a new drug product to earn a positive return on large, upfront R&D investment now required for FDA approval. (Grabowski, 2004; Grabowski, 2007)

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 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 upfront investments, with lessened concern over early litigation and generic entry.

B. Patent Reform Before the 110th Congress

Patent reform has become a significant issue facing the 110th Congress. Thomas & Schacht (2007) have written a Congressional Research Service (CRS) report which discusses House (H.R. 1908) and Senate (S. 1145) bills, the underlying patent reform proposals, and their relationship to innovation and the United States economy. The reform bills and the CRS monograph discuss these reforms, which include first-inventor-to-file, modifications of the willful infringement doctrine (which are both procedural and substantive), as well as new provisions for assignee filing, post-grant review, and pre-issuance publication of pending applications. Some of the reform issues have direct bearing on chemoprevention innovation and therefore merit further comment.

The proposed reforms include provisions intended to reduce patent litigation costs through changes to “willful infringement” damages, less expensive district court proceedings, and new post-grant review proceedings. The post-grant review reforms are particularly relevant to chemoprevention. These review mechanisms are modeled after U.S. trade partners’ practices

and are intended to strengthen patent quality and streamline opposition to patents early after their issuance, thus reducing court challenges and litigation costs. (Hall & Harhoff, 2004)

High quality patents are desirable in economic terms: new inventions which are non-obvious, useful, and novel receive short-term monopolies which provide adequate returns to inventors in return for their public disclosures. A monopoly awarded to a non-novel invention is a dead weight economic loss and creates a variety of undesirable consequences. Low quality patents introduce uncertainty regarding the defensibility of a patent which in turn can choke off investment. Low quality increases the number of patents sought and the resulting review load at the USPTO. Low quality also increases litigation.

Creation of a U.S. post-grant review process was one of the key recommendations to improve patent quality in a National Academy of Sciences (2004) sponsored report. Ideally, this process would provide the option of a less costly, more accessible, and streamlined mechanism compared to court-based litigation for challenging patents and determining their validity. The USPTO would hear and rule on the claims of a petitioner concerning patent invalidity that are filed within a prescribed period after patent issuance. The length of this filing period needs to balance adequate response time for petitioners against an undue wait burden for patent holders.

At the present time, the House and Senate patent reform bills have different provisions regarding the timing and procedures for post-grant review. (Lutton, 2007) The House bill (HR1908 as amended July 2007) would require that post-grant opposition be filed within 12 months of issuance (or later in time but only with the consent of the patent holder). There is no “second window” to post-grant review beyond this period, but the House bill would strengthen the existing *Inter Partes* re-examination process. (Lutton, 2007; Thomas & Schacht, 2007) By contrast, Senate bill 1145 allows for a “second window” of post-grant reviews. In particular, this

second window would be available when “the petitioner establishes in the petition a substantial reason to believe that the continued existence of the challenged claim in the petition causes, or is likely to cause, the petitioners significant economic harm.” This would likely be a relatively low bar for generic firms to meet in challenging patents and could be utilized strategically by these firms in an attempt to enter the market early before innovators have earned a return on their sizeable R&D investments. (Prasad, 2007)

An open-ended post-grant review period like that in the Senate bill would be especially problematic for pharmaceutical innovation, including chemoprevention. As discussed, commercially successful products in this industry are already subject to extensive patent challenges through paragraph IV filings under Hatch-Waxman. An open-ended post-grant review process would amplify the uncertainty surrounding the length of the market exclusivity period for innovative agents in the pharmaceutical industry. There is a balance to be struck between petitioners and patent holders in the nature and timing of post-grant reviews. An open-ended post-grant review period could pose a significant threat to investment in chemoprevention.

The number of patent challenges in the biosciences is likely to increase due to the recent Supreme Court decision (April 2007) *KSR International v. Teleflex, Inc.* The decision raises the standard for “non-obviousness” which is a central requirement in awarding a patent. While the *KSR* case was not a bioscience industry case, it has been interpreted by one opinion in the Court of Appeals for the Federal Circuit as applicable to the biopharmaceutical industry. In that opinion (*Pfizer v. Apotex*) the patent-holding firm, Pfizer, was required to show improved clinical efficacy for a molecule which lacked “structural novelty”. Patent litigation experts suggest the court is moving toward a more subjective test regarding what a person with ordinary creative skill in the art of biopharmaceutical sciences would do. (Harrison, 2007) This higher

standard may make existing patents vulnerable to challenges, thus increasing uncertainty for continued investment in clinical trials for new indications of existing drugs. It may also have the effect of making some new patents less certain or unobtainable and, therefore, more difficult or impossible to attract investment.

It is problematic that different industries are subjected to a “one size fits all” patent system, as patent law dictating scope of patent protection and requirements of patentability affect distinct industries in very unique ways. A pertinent example is the difference between the pharmaceutical and information technology industries. In the pharmaceutical sector, often only a few patents cover a particular drug product, that product is relatively easy to replicate, and the patent is a critical aspect of the business model that provides medical innovations, though it eventually allows for low-cost access by the public. These characteristics are vastly different from those of the information technology industry, where innovations are typically cumulative, the finished product often contains a multitude of patents, and ownership of the patents for that product are often divided among many players, including individuals and firms. (Thomas and Schacht, 2007) The application of various provisions of the patent law, therefore, can have very different effects across industries, such as information technology as contrasted with pharmaceuticals. (Pammoli and Rossi, 2005)

These differences also help to explain how different research-intensive industries can arrive at opposing positions with respect to provisions such as the timing of post-grant reviews, the apportionment of damages as well as the criteria for willful infringement by defendants, and inequitable conduct at the USPTO by claimants. Reflecting these tensions, all these provisions have undergone significant changes as the bills have evolved over time. (Lutton, 2007; Thelen Patent Law Portal, 2007) It remains to be seen whether Congress can bridge all the differences

across key stakeholders on these issues and craft a Patent Reform Act that broadly advances the goals of the patent system to foster innovation and market competition.

C. Prizes and Alternatives to Patents

Another policy option that has received attention by industry critics involves replacing patents with a prize from the government. (Hubbard and Love, 2004) A prize system has also been promoted as a creative way to stimulate R&D for “neglected diseases” like malaria. (Kremer, 2002; Ridley, Grabowski, and Moe, 2006) However, government-sponsored prizes appear to have many pitfalls as substitutes for the patent system in advanced economies. (DiMasi and Grabowski, 2007a) Most economists who have studied the R&D innovation area do not favor a government-awarded prize as a replacement to the patent system. One important reason is that a prize system would very likely provide inadequate incentives for long and costly research like that undertaken in pharmaceutical and biotech areas. Moreover, the Hubbard Love compulsory elimination of the patent system would have adverse consequences for pharmaceutical R&D, given the strong role that patents play in encouraging drug R&D and innovation.

Serious problems arise with government-sponsored prize mechanisms because the government is unlikely to be able to value innovations properly, while the incentives for innovators will depend crucially on how the government values innovations. Generally, private firms will be better informed about the potential value of innovations to consumers and providers. Prize systems are also subject to what economists have called the hold-up problem. The awards would typically be determined after an innovator has invested in developing an innovation. The temptation is great for the award-granting authority to offer prizes that are much

lower than the true value of the innovation. Since the innovator's costs are sunk, the innovator has little choice but to accede to the expropriation of value. Such behavior by the award-granting authorities, however, will greatly diminish the incentives for innovators to engage in future R&D activities. Therefore, it is unlikely that a generalized reward system could motivate as much risk-bearing as the patent system presently does. (DiMasi and Grabowski, 2004; DiMasi and Grabowski 2007a)

The Medical Innovation Prize Act of 2005, or H.R. 417 introduced by Congressman Bernie Sanders, also uses a prize mechanism as a non-voluntary substitute for patent exclusivity. It was intended to change the paradigms for financing medical R&D. This bill creates a shift away from relying on high drug prices as the incentive for R&D and towards directly rewarding innovators on the basis of the incremental therapeutic benefit to consumers through a new Medical Innovation Prize Fund. However, managing overall R&D incentives through a separate mechanism that can be increased or decreased depending on society's willingness to pay for medical R&D has the same problems as the aforementioned Hubbard Love prize. (OLPA, 2005)

While little evidence of broad political support exists for such radical change as prizes as alternatives to patents, this could be an important long-term issue for the biopharmaceutical industries. Though some foundations and prominent academics appear enamored by prize funds as a substitute for patents in the medical area to improve access and result in lower prices for new medicines, the cost of compulsory elimination of the patent system would likely be a significant stall in innovation and medical advancement.

V. POLICIES FOCUSED SPECIFICALLY ON CHEMOPREVENTION

A. 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. Public policies, of course, can involve a combination of both push and pull mechanisms. (Grabowski, 2005b)

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. By lowering R&D costs and risks, they help bridge the funding gap that characterizes the early stages of the R&D process. This funding gap can be particularly burdensome in the case of chemoprevention entities with their long time frames and above average clinical trial requirements. However, critics have pointed out that government grant programs and other push strategies can be an inefficient approach because of misaligned incentives and information related problems. (Kremer, 2002) This can occur because donors typically have less information than developers about which projects are most promising and which costs are most appropriate. It is important, therefore, that push strategies be designed in a way to avoid these incentive and information problems in order to increase the odds of successful outcomes from these programs.

The National Cancer Institute’s Division of Cancer Prevention has a contract-based drug development program which carries out preclinical and early clinical safety, pharmacology and efficacy testing. These “push” investments for research in chemoprevention are expected to decline in fiscal year 2007. (NCI, 2007) Priorities have been set with funding for existing trials involving tamoxifen and raloxifen (STAR trial), selenium and Vitamin E (SELECT Trial) and follow-up studies with finasteride. (NCI, 2006) As discussed previously regarding the NIH

funding gap, investments in existing chemoprevention studies such as STAR and SELECT are taking the majority of funds, leaving a lesser and declining amount (2007 compared with 2006) for new chemoprevention research in priority areas of colorectal, lung, esophageal, bladder, cervical, and oral cavity cancer. It will require vigilance by both government regulatory and external organizations to ensure these federal research investments are set using priorities that overcome the informational gap between the funder, NCI, and its recipients.

B. Lessons from the Orphan Drug Act

One successful policy measure involving push and pull mechanisms is the Orphan Drug ACT (ODA) 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 high costs of gaining FDA approval and more limited prospects of positive returns. The ODA contains three provisions to lower R&D costs. First, the ODA establishes a 50 percent 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 seven year market exclusivity that runs concurrently with any patent exclusivity terms applicable to particular drugs. This seven year market exclusivity is different than exclusivity provided under the patent system or the data exclusivity period provided under Hatch-Waxman. While it has

less breadth than a compound patent since it is specific to an orphan drug indication, it offers stronger protection from the standpoint that orphan drug exclusivity is not subject to patent challenges during the seven year period (or generic entry either through an ANDA or a regular NDA filing).

The Orphan Drug Act's primary incentive of a 50 percent 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 percent 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 productions for rare diseases have been brought to market since 1983. In contrast, the decade prior to 1983 saw fewer than ten 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. (Grabowski, 2005b) 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 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.

VI. 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. But 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. It is also important that policymakers avoid policies that would exacerbate the barriers to realizing the promises which these therapies hold out to current and future cancer patients. In this paper, we have presented several policy recommendations that reflect these twin objectives.

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Appendix 1 - MOLECULAR TARGETS AND AGENTS FOR CHEMOPREVENTION

| Molecular target | Clinical target | Representative agents |
|--|--|---|
| Anti-inflammatory/antioxidant | | |
| COX-2 | Multiple (colon, bladder, esophagus, lung, head and neck, breast, cervix, liver) | Celecoxib, rofecoxib, NSAIDs |
| EP ₁₋₄ | Breast, colon, head and neck | ONO-8711 |
| Inducible nitric oxide synthase/nitric oxide | Colon, prostate, bladder, head and neck | NO-NSAIDs |
| LOX | Lung, colon, esophagus | Zileuton, zafirkulast, licofelone |
| NF- κ B | Prostate, colon, head and neck, multiple myeloma, liver | Bortezomib, <i>R</i> -flurbiprofen, curcumin, tea polyphenols, statins, NSAIDs |
| Antioxidant response element (Nrf2) | Lung, head and neck | Dithiolthiones |
| Glutathione <i>S</i> -transferase | Lung, liver, head and neck | Dithiolthiones, PEITC |
| Nkx3.1 | Prostate | Tea polyphenols |
| Prostacyclin | Lung | Iloprost |
| Epigenetic modulation | | |
| DNA methylation | Prostate, lung | Azacytidine, folic acid |
| Histone deacetylase | Breast, colon | SAHA |
| Hormonal/nuclear receptor | Modulation | |
| 5 α -Steroid reductase | Prostate | Finasteride, dutasteride |
| AR | Prostate | Flutamide, bicalutamide, 3,3'-diindolymethane |
| Aromatase | Breast, prostate | Exemestane, letrozole, anastrozole |
| ER- α | Breast, prostate, colon | Tamoxifen, toremifene, arzoxifene, raloxifene, soy isoflavones, acolfibene, indole-3-carbinol, 3,3'-diindolymethane |
| ER- β | Prostate, colon, breast, ovary | Resveratrol, TAS-108 |
| Peroxisome proliferator-activated receptor- γ | Breast, colon, head and neck, liver | Rosiglitazone, pioglitazone, GW7845, CDDO, LGD100268 |

| | | |
|--|--|---|
| Retinoic acid receptor- β | Breast, ovary, colon, head and neck | Fenretinide, 9- <i>cis</i> -retinoic acid |
| Retinoic acid receptor/retinoid X receptor | Breast, skin, head and neck | 9- <i>cis</i> -Retinoic acid |
| Retinoid X receptor | Breast | Targretin, LGD100268 |
| VDR | Colon, prostate | Vitamin D3 analogues |
| Signal transduction modulation | | |
| BCL-2 | Colon, prostate | ABT-737 |
| Cyclic guanosine 3',5'-monophosphate PDE | Prostate, colon | Exisulind |
| Cyclin D1 | Head and neck, esophagus | |
| EGFR | Lung, bladder, breast, colon | Gefitinib, erlotinib, EKB569, cetuximab |
| HMGCoA reductase | Colon, skin (melanoma), breast, prostate | Statins |
| IGF/IGF receptor | Breast, colon, prostate | |
| MAPK | Head and neck, lung, breast, bladder | |
| Matrix metalloproteinases | Colon | Marimistat, prinomastat |
| mTOR | Prostate | RAD-001 |
| Ornithine decarboxylase, polyamine synthesis | Colon, bladder, skin | DFMO |
| p53 | Lung, esophagus, head and neck | CP31398 |
| PI3K/AKT, PTEN | Head and neck, lung | Deguelin, LGD100268 |
| <i>ras</i> | Colon, pancreas, lung | Tipifarnib, perillyl alcohol |
| Transforming growth factor- β /SMADs | Breast | CDDO |
| VEGF/VEGF receptor | Colon, breast | Bevacizumab |

(Source: Kelloff et al, 2006)

Appendix 2 - BIOGRAPHICAL SKETCHES OF THE AUTHORS

1) *Henry Grabowski*

Henry Grabowski is currently Professor of Economics and the Director of the Program in Pharmaceuticals and Health Economics at Duke University. He has studied the economics of the pharmaceutical industry over much of his career, and has published numerous articles and books on this industry. Under a series of grants from the national Science Foundation he has examined the economics of pharmaceutical research and development (R&D) and the effect of various government policy action on drug innovation. He has testified several times before Congressional committees in the United States on pharmaceutical industry issues. For example, since 1994, he has testified on issues involving effective patent life and generic competition in pharmaceuticals, the Clinton Administration's health reform legislation, and the federal government's policy toward children's vaccines.

He has been an advisor and consultant to the National Academy of Sciences, the Institute of Medicine, the Federal Trade Commission, the General Accounting Office and the Office of Technology Assessment. He also held visiting scholar appointments at the International Institute of Management in Berlin, Germany, the Health Care Financing Administration in Washington, DC, the Office of Health Economics in London, and the Centre for Medicines Research in London. Until its acquisition by Gilead Sciences in 2003, he served on the Board of Directors of Triangle Pharmaceuticals, Inc., a development-stage company that specialized in antiviral drug therapies.

He has done extensive research on the economics of competition in the drug industry, including the role of patents and the importance of research and development.

He has also performed several studies on R&D costs and returns in pharmaceuticals. The Congressional Budget Office has utilized this work to analyze the effects of the Hatch-Waxman Act on RD returns, and to analyze the proposed changes associated with the Clinton Health Reform Act of 1993.

2) *Jeffrey Moe*

Jeffrey Moe is an Adjunct Associate Professor in the Health Sector Management program, the Fuqua School of Business, Duke University. He joined the faculty in 2001 after a career in consulting and the pharmaceutical industry. Among his faculty responsibilities, Professor Moe co-teaches the “Strategy and Economics of the Pharmaceutical Industry” (HLTHMGMT 409). The role of patents, the economic trade-offs associated with various U.S. Federal policies and legislation (e.g. Orphan Drug Act) and more broadly, the dynamics between generic and pioneer manufacturers regarding patents are among topics covered in this course.

His research interests include the diffusion of clinical guidelines at the point of care, under-investment in R&D for neglected diseases, the commercialization of pharmacogenomics and pricing and reimbursement issues for health care products. Dr. Moe’s lecture, “Commercialization Considerations for Individualized Diagnostic and Drug Therapies Resulting from Pharmacogenomics” was published in the *Louisiana Law Review*, December 2005. He and his colleagues, Henry Grabowski and David Ridley published their paper, “Developing Drugs for Developing Countries”, March/April, 2006, *Health Affairs*. Subsequent to the publication of that paper, Senators Brownback (R-KS) and Brown (D-OH) conferred with the Duke researchers and introduced an amendment

(SEC. 524. PRIORITY REVIEW TO ENCOURAGE TREATMENTS FOR TROPICAL DISEASES) modeled after their proposed incentive into the Food and Drug Administration Revitalization Act (S.1082) which passed May 9, 2007. A similar “priority review voucher” amendment was included in H.R. 3580, the Food and Drug Administration Amendments Act of 2007, as a result of the House and Senate conference, and was signed into law on September 27, 2007 by President Bush.

As Principal Investigator on a National Cancer Institute grant, he traveled in June 2005 to Amman, Jordan to collect data for a descriptive study of the King Hussein Cancer Center, an innovative and recent example of a “transnational health organization”. “Transformational leadership, transnational culture and political competence in globalizing health care services: a case study of Jordan’s King Hussein Cancer Center” is in press at *Globalization and Health*.

Professor Moe also serves as Senior Director, Business Development for the Health Sector Management program. In that role he develops collaborations between the university and healthcare organizations to pursue problem-centered and theoretical research drawing upon multiple disciplines including medicine, business, law, economics and public policy.

Before coming to Duke in 2001, Professor Moe was an executive at GlaxoSmithKline. Over a 15-year career he held positions in business development, corporate strategy, marketing, market economics and human resources.