Abstract

High quality new molecular entities (NMEs) are drug therapies that provide the most value to the public and are the measure of innovation within the pharmaceutical industry. However, these drugs are not the most profitable for the industry and the pipeline appears to be slowing. Thus, high quality NMEs represent a positive externality in the pharmaceutical market. In this paper I examine the status quo and two policy alternatives: creating a Translational Research Center within the National Institutes of Health to directly increase the number of high quality NMEs, and changing regulations at the Center for Drug Evaluation and Research to incentivize industry to increase the number of high quality NMEs. Due to the complexities of research and development as well as the pharmaceuticals market, I recommend that the federal government create a Translational Research Center.

Introduction

High quality new molecular entities (NMEs) are drug therapies with novel chemical formulations that offer more effective or less harmful treatments than previous therapies—including effective therapies for previously untreated diseases. The most profitable drugs for the pharmaceutical industry, however, are generally not novel chemical formulations. Because NMEs do not provide the greatest benefit for the pharmaceutical industry but do provide a benefit beyond their market valuation, high quality NMEs represent a positive externality in the pharmaceuticals market.

‡ Alex Hartzman is a masters candidate (2012) in the public health and public affairs programs at the University of Wisconsin - Madison and works in the public health emergency preparedness unit at the Wisconsin Department of Health Services. In 2010 he was the first recipient of the Ina Jo Rosenberg and Shiri Eve Leah Gumbiner Fellowship for health policy studies. Prior to his masters education, Alex worked as a student health advocate at the Center for Patient Partnerships. He holds a Bachelor of Science in Astro-physics and Physics (2009), also from UW-Madison.
The pharmaceutical industry chooses what diseases and treatments to pursue based largely on the state of research and how it perceives consumer demand. This varies by firm, both in terms of their research capabilities and market studies. There is no discernible trend over the last thirty years, but there are typically at least 50 non-NMEs approved each year.\textsuperscript{ii} Most of these are reformulations or new-use approvals for existing drugs. New formulations of existing drugs are awarded an additional three years of patent protection under the 1984 Hatch-Waxman Act. This incentivizes firms to continue investing in existing drugs to extend their profitability instead of making larger investments on NMEs in a research and development (R&D) gamble.\textsuperscript{iii}

Pharmaceutical R&D is costly and time consuming. On average, it takes 11.8 years and between $500 million and $2,000 million (typically $868 million) for a drug to be brought from discovery to approval.\textsuperscript{iv} Moreover, R&D expenditures are rising as a result of the increasing costs of running clinical trials and the increasing rates of failure.\textsuperscript{v} Pharmaceutical industry R&D spending has increased roughly 5 percent per year from 1980 ($5.5 billion) to 2003 ($17 billion).\textsuperscript{vi} As of 2008, the market share for generic drugs (off-patent therapies with nonproprietary names) has increased to 58 percent. As a result, R&D investment is expected to decrease, since manufacturers pursue drugs primarily based on expected revenue returns.\textsuperscript{vii}

Pharmaceutical companies cannot predict which NMEs will be high quality, let alone generally efficacious or harmful. They also cannot predict which ones will receive Center for Drug Evaluation and Research (CDER)\textsuperscript{viii} approval. This may partly explain the variation (currently a downward trend) in the number of high quality NMEs produced by the industry: the proportion of high quality NMEs to other NMEs has dropped from 14.8 percent (annual average 1989-2000) to 10.7 percent (annual average 2000-2004).\textsuperscript{ix} Furthermore, CDER received fewer NME applications in 2010 than it has in any of the previous fifteen years, illustrating a continuous downward trend.\textsuperscript{x}

The industry is increasing its focus on novel therapies to treat rare diseases\textsuperscript{xii} There are several difficulties inherent to creating a medication for a rare disease, regardless of the disease itself. Mainly, having a disease with fewer patients means a much smaller population to get a good sample size for study, which can severely hamper attempts to prove a medication’s efficacy or hide potential confounders and side effects.\textsuperscript{xii}

NMEs (high quality or not) are not necessarily the most profitable drugs for the pharmaceutical industry. The industry earns a large proportion of its
profits from follow-on drugs, such as Nexium, that provide extremely similar therapies to drugs already in use. The industry also profits from extending the patents on existing successful medications through reformulations, new dosing, and discovery of new uses.\textsuperscript{xiii} This difference in preferences indicates a potential market failure as NMEs present a positive externality: the potential benefit to society is greater than the market incentives for industry to produce them. This suggests that government intervention would benefit consumers.

In comparing two alternatives to the status quo, I first address policy goals and impacts, followed by the criteria I use in my analysis. The next section examines the status quo, a Translational Research Center (TRC) within the National Institutes of Health (NIH), and restructuring CDER rules. The paper concludes with my recommendation.

**Policy Goals and Impacts**

The policy alternatives proposed are specifically intended to increase the number of high quality NMEs available to consumers without affecting safety and efficacy regulations. The policy alternatives are evaluated on the following criteria:

- Increase the number of NMEs submitted to CDER. Increasing the total number of NMEs submitted increases the likelihood of developing high quality NMEs.
- Diversify the research and development of new drugs with an emphasis on novel treatment of rare diseases. A simple increase in the number of NMEs produced by the industry will not address the externality if they do not provide treatment for a wider array of conditions.
- Minimize costs to the consumer. This improves accessibility to beneficial drugs, including potentially life-saving treatments.
- Ensure political feasibility. Feasibility is dependent on industry acceptance, political opinions, and costs to taxpayers. Industry acceptance is particularly important because of the strength of the pharmaceutical lobby.
Alternative 1: Maintain the Status Quo

Overview

The pharmaceutical industry researches, designs, markets, and manufactures a wide variety of therapies to treat numerous diseases. Firms are heterogeneous: they vary in size and differ in capabilities in terms of discovery, R&D, marketing, legal staff, etc. The scope of this paper is to look at the industry as a whole, trends within it, and how potential policies may affect it. The relational picture of changing profits, R&D investment, and industry NME output is complex, but seems to point to a recent decline in innovation.

This section seeks to provide a base to be compared with the two alternatives, where applicable. The policy goals and impacts are not so much departures from the status quo as they are improvements in the market from the current state – status quo realities may contain trends or mechanisms that will correct the market to achieve these desired goals and impacts.

Number of NMEs

The industry is submitting fewer NMEs for approval. It remains to be seen how this trend will affect the number of approved NMEs over the next several years. In 2010, the pharmaceutical industry submitted 23 applications, the second lowest in fifteen years (range: 22 in 2002 to 45 in 1996). There is an overall downward trend in the numbers of NMEs submitted for approval each year. Not all drugs submitted to the approval process are approved; CDER has approved an average of 22.9 NMEs per year over the last 15 years. Many of the drugs that are approved require post-marketing studies; it is impossible at this point to say how many will be higher quality than competing therapies.

Gross industry profits are strongly correlated with R&D investment. As the industry is becoming less profitable – many of the industry’s top-selling drugs are coming off patent and will face direct competition from generic drugs at lower prices – we can reasonably expect R&D expenditures to lower in response. Some analysts argue that the effects of insurance (hiding the true cost of drugs from consumers, leading them to over utilize drugs) and marketing (creating demand) have caused the pharmaceutical industry to misread profits as consumer demand and overinvest in non-NME R&D as a response.
Research and development of novel therapies

Basic research – the foundational research at the root of discovery – is typically done by biotechnology firms, universities, NIH, ethnobotanists, etc. These discoveries are then released to or purchased by the pharmaceutical industry, which translates that basic chemical discovery into applications. NMEs are created wholly within the pharmaceutical industry. These drugs tend to generate more revenue than their externally discovered counterparts but are substantially less likely to be innovative or “respond to unmet medical needs.”

Cost to consumers for newly approved NMEs

Cost to consumers is based on R&D, manufacturing, marketing and other costs, threats of government regulation, world market fluctuations as well as consumer willingness-to-pay and price tolerance studies in some cases. An NME for a previously untreated disease can be viewed essentially as a monopoly, as there are no competing or substitutable therapies. Under these conditions, firms have full control of consumer prices.

Prices charged to consumers for a newly approved NME vary by therapy, but tend to be expensive for first-in-class life-saving medication. An extreme example of this is Alexion Pharmaceutical’s Soliris which treats paroxysmal nocturnal hemoglobinuria (a disease which affects only 8,000 Americans). It is the most expensive drug currently on the market at a consumer cost of $409,500 for a year of treatment. There are now over nine drugs that cost over $200,000 per year.

Political feasibility

It is typically acceptable to maintain the status quo for a variety of well-studied political and economic reasons, none of which this paper will discuss. Each alternative will have a discussion of the apparent political feasibility to move away from the status quo.

Alternative 2: Create an NIH Translational Research Center

Overview

This alternative creates a Translational Research Center (TRC) within the National Institutes of Health (NIH) with the mission of researching and
developing new therapies. Specifically, it would develop therapies that industry will not produce due to slow uptake of new techniques and basic research discoveries of NIH or to unwillingness because of the size of the potential market. This division would thus translate basic research into applied research to minimize the time from discovery to dissemination of new medicines. The TRC would decide which diseases to target based on its assessment of the needs of the populace, the state of basic research as it relates to a potential therapy, and whether the industry is pursuing a similar medication. The TRC would consist of new or repurposed labs at NIH campuses and the materials and personnel to fully utilize them. Additionally, the TRC would coordinate already existing grants and university-based translational research work being done with NIH in order to form complementary capabilities across multiple partners.

The TRC would not manufacture the drugs it designs. Instead, manufacturing would be contracted out to the industry to avoid large startup costs. It would also provide industry with R&D assistance and funnel them partial discoveries. This process could be complicated and would require rules that govern how the TRC interacts with industry in terms of both collaboration and staff bleed-over. The TRC would maintain control of patents in order to keep authority over drug distribution as well as to ensure it follows the same testing standards as the industry.

**Number of NMEs**

The TRC would increase the number of NMEs by developing its own without detracting from the number of therapies that industry produces. However, the extent to which the TRC will directly increase the number of high quality NMEs available to consumers is uncertain because pharmaceutical R&D cannot produce guaranteed results. Because the TRC will focus on novel therapies for untreated or undertreated diseases, any successes would provide to consumers NMEs that are high quality by definition.

The mission of the TRC is consistent with creating medications to combat diseases that have a low demand-to-R&D-cost ratio, which tend to be low-incidence diseases. As such, diseases the TRC targets will be unlikely to have competing therapies within the industry, as those medications would not be commercially viable. Some therapies the TRC develops would likely be substitutes for existing medications, but otherwise the center and industry would not compete. Therefore, industry would largely continue to submit
the same number of NMEs to CDER and all TRC submissions would be an increase in the total number of NMEs submitted for approval.

The mission to translate basic research into clinical research will involve sharing some research and discoveries with the industry. The NIH already conducts much of the basic research that goes into pharmaceutical development, and the new division would continue these ties. Further developing the NIH’s basic research before giving it to industry should speed the industry’s efforts to create NMEs.

**Research and development of novel therapies**

The TRC’s primary focus would be to develop NMEs available for patients with rare diseases. The TRC will research and design new drugs and therapies that have either not been pursued by the pharmaceutical industry or that the industry has otherwise failed to produce. Additionally, it will supply industry with semi-developed research to open the pipeline of drugs for these patients over and above the industry’s increasing focus on therapies for relatively rare and small-market diseases.

**Cost to consumers for newly approved NMEs**

Establishing the TRC should yield drug costs substantially lower than what industry would charge. The TRC would determine pricing of NMEs, as it would maintain control of the relevant patents and the manufacturing and distribution process. As the TRC would be a public entity that has a primary objective of creating NMEs, center administrators would decide the cost to consumers, and therefore it would reflect actual development costs rather than profit-seeking.\(^{xxv}\)

**Political feasibility**

Political opinion on the TRC is uncertain. Spending is an issue in the current budget climate, but the impetus to rein in pharmaceutical costs and increase the number of NMEs may outweigh these concerns. The TRC may be at least partially funded by consolidating current government R&D programs and reducing grants. It will be attractive if it requires little new funding, though budget implementation would be in the hands of NIH and Department of
Health and Human Services (HHS) chiefs as well as Congressional stakeholders.

Upfront costs to taxpayers would be roughly $1.3 billion for startup facilities, personnel, and materials. Part of this would come from consolidation of current government-sponsored pharmaceutical research, most likely much more than the $378 million spent in 1993. While this startup cost is high, it is comparatively little next to the average cost of industry NME development. Additionally, investing in the process should prove more efficient than investing in individual industry projects as this has proven difficult in the past.

Creating a new NIH division will present many difficulties, including hiring a staff of researchers, maintaining a steady funding source from Congressional stakeholders and other NIH and HHS administrators, acquiring the appropriate equipment and materials, and deciding what diseases and therapies to pursue. The costs of initial inefficiencies inherent in the creation of such projects are difficult to project at this time.

Industry acceptance of the TRC is ambiguous. The industry and the TRC will not be direct competitors; the TRC will most likely develop therapies for underserved markets while industry will continue to focus on the most profitable therapies. It should be noted that if the TRC creates a drug with market potential, the industry would likely put money into R&D for a substitute or follow-on medicine in order to capture potential consumers. In this case, the industry would directly compete with the TRC and would use resources to create therapies that treat the same disease instead of the intended novel therapies for untreated or undertreated diseases. The creation of the TRC is a boon to the industry as a whole: it effectively takes R&D a step further before handing it over to pharmaceutical firms. However, firms doing translational research may view it as unwanted competition. This policy alternative will not change the power or rights of the patent holding entity, as FDA rules will be unaffected and the TRC will put its drugs through the same testing process as the industry.

The pharmaceutical industry relies on outside research for drug discovery—universities were responsible for roughly 31 percent of novel drug discoveries between 1998 and 2007. Thus, it would be likely to accept further help from non-industry sources.
Alternative 3: More Stringent CDER Regulations

Overview

A second alternative to the status quo would be to change CDER regulations to require that drugs submitted for approval have high quality or, for drugs that cannot be assessed without post-marketing studies, at least demonstrate strong indications of high quality. In other words, they must be more effective or less harmful than an already existing therapy.

CDER’s main task is to use physician, statistician, chemist, pharmacologist and other scientist expertise to evaluate studies of drugs that pharmaceutical companies submit for approval. This process requires studies to demonstrate that a drug’s health benefit outweighs its known risk. However, there is a major weakness in CDER’s basic mission that must be addressed to increase the supply of high quality NMEs. Namely, a drug must only be proven more beneficial than harmful (i.e., it must show more effectiveness than a placebo), not that it must be more beneficial or less harmful than already existing therapies.

There are other problems with the CDER drug approval process: the companies that have a stake in the results often conduct the studies, surrogate measures are often approved (e.g. reducing a risk factor, but not requiring proof that this reduces the incidence of the targeted disease), and there is weak enforcement of required post-marketing studies.

Number of NMEs

This policy change should increase the proportion of high quality NMEs to other drugs by not allowing less effective or more harmful (compared to an existing therapy) NMEs onto the market. By nature, if an NME is a novel therapy, it will be considered high quality. Thus, firms will be more likely to research and develop NMEs if their chances of approval are higher.

Research and development of novel therapies

Follow-on drugs are more often the result of a development race than imitation: in the 1990s, 88 percent of as yet unapproved first-in-class drugs had follow-ons in the same class in Phase 3 clinical trials. The mechanisms by which a development race (or imitation research) start is unclear. As such, it is not possible to predict whether this policy would discourage direct competition
from follow-on drugs or merely result in further studies to differentiate a follow-on drug from the first-in-class therapy. Weighing the approval process in favor of novel therapies should incentivize pharmaceutical companies to pursue NMEs that would serve previously untreated or rare diseases.

**Cost to consumers for newly approved NMEs**

Costs to consumers may increase slightly because this alternative increases the value of NMEs over already approved compounds, and it will require more R&D to discover a larger number of NMEs. Consumer cost of drugs will continue to depend on industry willingness-to-pay studies and the nature of the diseases treated, such as the efficacy of the current treatment if one exists and how many people are afflicted with it. Such a policy may increase industry reliance on biomedical companies and universities, which discovered about 56 percent of scientifically novel NMEs (35 percent of all NMEs) from 1998 to 2007. This reliance could either increase or decrease costs, depending on the discovery efficiency of pharmaceutical companies as compared to biomedical companies and universities.xxxiii

**Political feasibility**

The political feasibility of this policy change is difficult to predict. The rule change itself should not incur a major administrative cost on the government. The pharmaceutical industry has a very strong lobbying presence and would fight the change because it would make approval for non-novel therapies significantly harder to obtain.

This policy change would likely increase the value of a drug patent as it would make drug approval harder to obtain, particularly for follow-on drugs. Follow-on drugs would have to go through further studies to demonstrate increased effectiveness over the first-in-class drug, either overall or for specific populations. This would increase the value of the first patent by the cost of additional studies, perhaps inciting a race to application for the CDER approval process. In some cases where first-in-class drugs and their follow-ons have similar efficacy across all patient groups, that particular race would be winner-take-all.

This policy alternative would require no additional up-front cost to taxpayers from the status quo. Additionally, this policy would be a substantive rules change that would require no difference in technical expertise of CDER
personnel from the status quo, so administrative costs should remain the same.

Recommendation

I recommend that Congress create a Translational Research Center within NIH. A consolidated, government-run Translational Research Center would both provide high quality NMEs directly to the market at lower costs than industry and funnel discoveries into industry. This would benefit both the population and the drug industry.

Endnotes

i. New Molecular Entities are drugs that contain no active moiety that has been approved by the FDA


ix. CDER is a division of the US Food and Drug Administration (FDA)


xii. Conway, B. “Big Pharma Reassesses Orphan Drug Sector.” Genetic Engineering &
**Biotechnology News**, March 1, 2011


xxii. *Undertreated refers to a disease whose therapy is of limited effectiveness or causes excessive harm.*

xxiii. Additionally, most follow-on drugs are researched simultaneously with the first-in-class therapy and not purely as a response to a successful first-in-class drug (DiMassi, 2011).

xxiv. *It is plausible that the industry and the TRC may compete over talent. However, if the industry downsizes its R&D departments as is implied by this analysis, there will be an oversupply of researchers and support staff for just the industry to hire.*

xxv. *Pricing could be used to offset some portion of the production cost or we could consider a pricing system under which the federal money is considered a direct subsidy and consumers/insurance pay the rest. Pricing will depend on the fiscal security of the TRC. That said, unlike industry it will not be trying to earn a profit, so at most*
NMEs developed by the TRC will be priced an amount related to the research and production cost.

xxvi. Ibid


